Stephen Gough
Editor

Handbook of Incretin-Based Therapies in Type 2 Diabetes

Adis

Handbook of Incretin-based Therapies in Type 2 Diabetes

Editor
Stephen Gough

Handbook of Incretin-based Therapies in Type 2 Diabetes

Adis

Editor
Professor Stephen Gough
Oxford Centre for Diabetes, Endocrinology and Metabolism
Oxford University
Oxford, United Kingdom

ISBN 978-3-319-08981-2 ISBN 978-3-319-08982-9
DOI 10.1007/978-3-319-08982-9

Printed on acid-free paper

This Adis imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Project editor: Katrina Dorn

Contents

Contributors

Carolyn F Deacon
University of Copenhagen
Denmark

Archana Dhere
University of Oxford
United Kingdom

Baptist Gallwitz
University of Tübingen
Germany

Robert R Henry
University of California at San Diego
United States

Jens Juul Holst
University of Copenhagen
Denmark

Eduard Montanya
University of Barcelona
Spain

Sunder Mudaliar
University of California at San Diego
United States

Editor biography

Stephen Gough is Professor of Diabetes at the University of Oxford and Consultant Physician at the Oxford University Hospitals NHS Trust. Professor Gough graduated in medicine from Leeds University Medical School, where he was later awarded a higher degree Doctorate in Medicine, which focused on cardiac dysfunction and abnormalities in coagulation and fibrinolysis present at the time of diagnosis of type 2 diabetes. He is currently based at the Oxford Centre for Diabetes, Endocrinology and Metabolism, where he is a practicing clinician in diabetes. His research interests and ongoing research studies include translational aspects of diabetes, with a focus on the physiology of islet cell and whole organ pancreas transplantation, incretin biology, and incretin therapies in diabetes. Professor Gough has previously had a strong interest in the genetic susceptibility to autoimmunity and this work has been extended into his work on pancreas transplantation. He has published his research extensively in peer-reviewed journals and has contributed to many national and international conferences and books on diabetes. In recent years, Professor Gough has helped develop translation research in diabetes in Oxford through a number of local and national initiatives, including the Oxford Biomedical Research Centre ,and he is Clinical Lead in Diabetes for the Oxford Academic Health Science Network and the Oxford Local Clinical Research Network.

Addendum

Since editing this book, Professor Gough has taken up the position of Senior Principal Clinical Scientist with Novo Nordisk. He continues as Visiting Professor of Diabetes at the University of Oxford and Honorary Consultant with the Oxford University Hospitals NHS Trust.

Chapter 1

Introduction and disease overview

Sunder Mudaliar, Robert R Henry

The term 'epidemic' has evolved dramatically from its first use by Homer and Hippocrates, through the Middle Ages when it defined the rapid propagation of diseases like the plague, to the 19th century when it was used to describe infectious diseases, and later in the 20th century where the term is applied to noninfectious diseases such as obesity and type 2 diabetes [1]. Today, type 2 diabetes is not merely an epidemic but a pandemic that is prevalent across most countries and continents. The International Diabetes Federation (IDF) estimated that in 2013, diabetes affected more than 382 million people worldwide and by 2035, nearly 592 million people will be diagnosed with this debilitating disease, with enormous social and economic implications [2].

The core pathophysiologic defects which contribute to the development of hyperglycemia in patients with type 2 diabetes include insulin resistance in muscle and liver and impaired β-cell insulin secretion. In addition to these defects, other abnormalities such as accelerated lipolysis in the adipocytes, impaired incretin action in the gastrointestinal tract, hyperglucagonemia secondary to α-cell dysfunction, increased renal glucose reabsorption, and insulin resistance in the brain also play important roles in the development of glucose intolerance in individuals with type 2 diabetes. These abnormalities have been collectively termed the 'ominous octet' [3].

Chronic hyperglycemia leads to the development of the characteristic microvascular complications such as retinopathy, nephropathy and neuropathy, and macrovascular complications such as premature

S. Gough (ed.), *Handbook of Incretin-based Therapies in Type 2 Diabetes*, DOI 10.1007/978-3-319-08982-9_1

cardiovascular disease (CVD). The microvascular complications lead to blindness, end-stage kidney disease, and amputations, while the macrovascular complications lead to premature cardiovascular morbidity (eg, myocardial infarctions and strokes) and excess cardiovascular mortality [4].

However, the development of diabetic complications is not inevitable. The United Kingdom Prospective Diabetes Study (UKPDS) was the first large scale study in patients with type 2 diabetes to show that intensive glucose lowering to a mean glycated hemoglobin (HbA1C) level of 7% was associated with a significant 25% reduction in the incidence of microvascular complications [5]. A 10-year post-trial follow-up of the original UKPDS cohort demonstrated that, despite an early loss of glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed [6]. The persistence of vascular benefits in the long-term despite the loss of any glycemic differences between the intensive and conventionally treated groups has been termed the 'legacy effect.' It is important to note that the UKPDS studied patients with newly diagnosed type 2 diabetes in whom early intensive control lowered the risk for microvascular complications in the short-term and was associated with a lower risk for macrovascular disease in the long-term.

In contrast to the UKPDS, the ACCORD, ADVANCE, and the Veterans Affairs Diabetes Trial (VADT) studies showed that although lower A1C levels (in the range of 6.4–6.9%) were associated with reduced onset or progression of microvascular complications, there was no significant reduction in CVD outcomes with intensive glycemic control in participants who had more advanced type 2 diabetes and either known CVD or multiple cardiovascular risk factors [7–9]. Also, in the ACCORD study, as compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels (6.4 vs 7.5%) for 3.5 years was associated with a 22% increased risk of all-cause mortality [9]. These findings suggest a previously unrecognized harm of intensive glucose-lowering in high-risk patients with type 2 diabetes, especially in those with a long duration of diabetes, known history of severe hypoglycemia, advanced atherosclerosis, and advanced age/frailty who may benefit from less aggressive targets.

Based on the results of these studies, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend that diabetes providers should aim to reduce HbA1C to around 7% without undue side effects [4]. In younger patients or in those with short duration of diabetes, long life expectancy, and no significant CVD, HbA1C can be reduced to a lower target (<6.5%) if it can be achieved safely with minimal risk for hypoglycemia and weight gain. In older patients and in those with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, a less stringent HbA1C goal (such <8%) may be appropriate. In all cases, severe or frequent hypoglycemia should be an absolute indication for the modification of treatment regimens and setting higher glycemic goals. The ADA/EASD guidelines also recommend fasting capillary plasma glucose in the 70–130 mg/dL range and peak post-prandial capillary plasma glucose <180 mg/dL. The IDF glycemic goals are similar to the ADA/EASD goals and recommend goals of:

- HbA1C<7.0% (53 mmol/mol);
- fasting/pre-meal capillary plasma glucose of approximately 6.5 mmol/L (115 mg/dL); and
- post-meal capillary plasma glucose of approximately 9.0 mmol/L (160 mg/dL) [10].

The American Association of Clinical Endocrinologists (AACE) recommends individualizing glycemic goals on the basis of age, comorbidities, duration of disease, with a target HbA1C level of ≤6.5% for most non-pregnant adults, if it can be achieved safely, but less stringent for less healthy patients. To achieve this target HbA1C level, AACE recommends that fasting plasma glucose (FPG) should usually be <110 mg/dL and the 2-hour post-prandial glucose concentration should be <140 mg/dL [11]. In order to obtain an optimal individualized HbA1C goal, all patients with type 2 diabetes should be encouraged to pursue healthy lifestyle measures including a consistent carbohydrate diet and regular appropriate exercise. When lifestyle measures fail to improve glycemic control, patients will need to take antidiabetic agents.

Today, there are a dozen classes of agents to treat type 2 diabetes and several newer agents are in clinical trials (Figure 1.1). The oldest

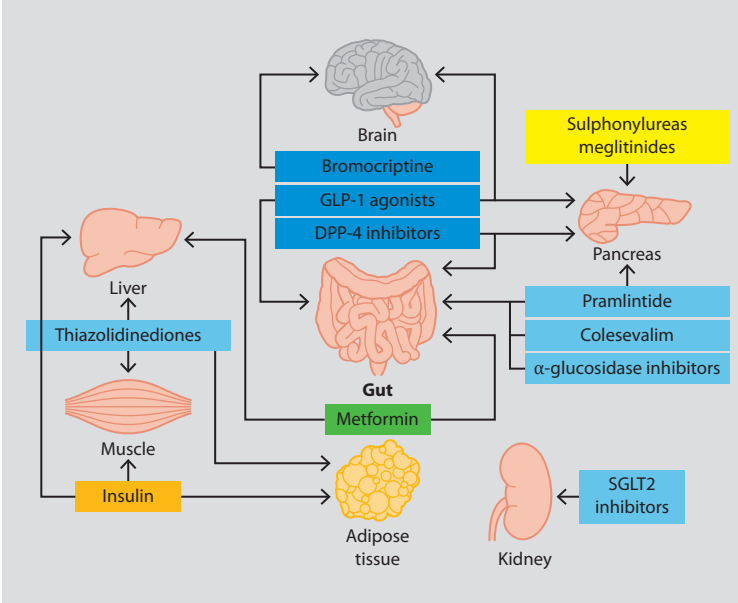

Figure 1.1 Glucose-lowering agents. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide; SGLT2, sodium-glucose cotransporter 2.

agent, insulin, was first introduced in 1922. For many decades, injectable insulin remained the only therapeutic option until the availability of the orally administered sulfonylureas in the 1950s. These drugs stimulate pancreatic β cells to secrete insulin by binding to receptors that block the potassium adenosine triphosphate (ATP)-dependent channels. Although both insulin and sulfonylureas are effective in lowering blood glucose, their use is associated with weight gain and a significant increase in the risk for hypoglycemia, especially in patients who delay or miss meals.

An alternative strategy to lower blood glucose is to improve muscle and hepatic insulin sensitivity and reduce insulin resistance. Metformin, a biguanide, effectively inhibits hepatic glucose production, while thiazolidinediones are potent insulin sensitizers. Both agents effectively lower blood glucose and have a lower risk for hypoglycemia because they do not stimulate insulin secretion but instead, lower insulin levels. Metformin in addition is associated with either a neutral effect on body weight or modest weight loss, while the thiazolidinediones increase body weight.

In addition, the thiazolidinediones are also associated with undesirable side effects such as pedal edema, precipitation of heart failure, bone fractures, and controversies over their effects on CVD. This has led to a decline in the use of these agents, while metformin use is widely prevalent except in the case of patients with renal insufficiency, which increases the risk for lactic acidosis.

Other anti-diabetic drugs include the α-glucosidase inhibitors which blunt intestinal glucose absorption: parenteral pramlintide, an amylin analog which decreases glucagon and slows gut motility; colosevelam, a bile acid sequestrant with a still-unclear mechanism of action; bromocriptine, a dopaminergic agonist; incretin-based agents (glucagon-like peptide [GLP]-1 receptor agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors), and sodium-glucose cotransporter 2 (SGLT2) inhibitors which promote renal glucose excretion. It is important to note that all of the above agents do not increase the risk for hypoglycemia. In addition to hypoglycemia, the other major factor which influences the use of anti-diabetic agents is weight gain. All the above agents are either weight neutral or they promote modest weight loss. Among the above agents, the incretins and the SGLT2 inhibitors have generated the most interest in the diabetes community due to their unique mechanisms of action.

The incretins, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), are neuroendocrine hormones which have pleitropic effects and exert their effects through interaction with G protein-coupled receptors [12]. Activation of GLP-1 receptors leads to glucose-dependent insulin secretion, inhibition of glucagon secretion, delayed gastric emptying, decreased appetite/increased satiety, and other potential beneficial effects on the cardiovascular system and central nervous system (in animal studies) (Figure 1.2). A major therapeutic hurdle with the use of the incretins is that circulating levels of the endogenous incretins decrease rapidly after secretion into the circulation because of enzymatic inactivation, mainly by DPP-4.

This has been overcome through the use of incretin mimetics (eg, exenatide, liraglutide, albiglutide, dulaglutide, and lixisenatide), which are GLP-1 receptor agonists resistant to DPP-4 degradation; and the DPP-4 inhibitors (eg, alogliptin, linagliptin, saxagliptin, sitagliptin, and

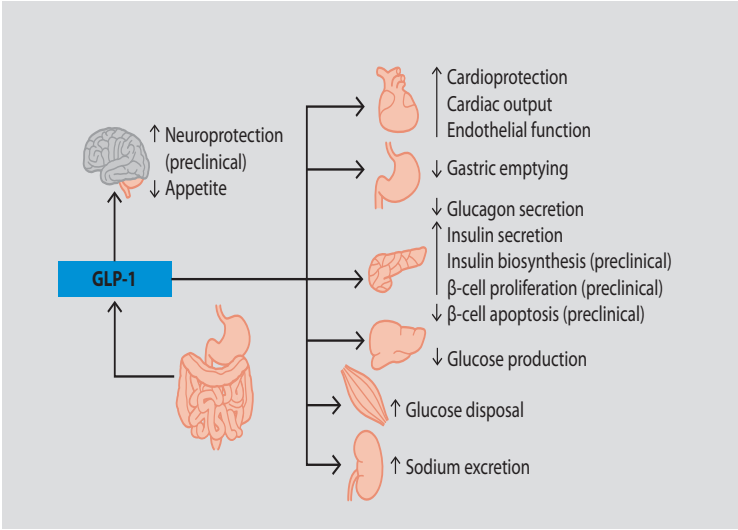

Figure 1.2 Physiological actions of glucagon-like peptide-1 (GLP-1).

vildagliptin), which potentiate the effect of the incretin hormones by competitively inhibiting the enzyme responsible for their degradation (Figure 1.3 and Table 1.1). The ability of the incretin agents to improve glycaemia with a low associated risk of hypoglycemia, together with beneficial/neutral effects on body weight, offers a significant advantage for both patients and treating clinicians [11].

Most clinical guidelines (ADA/EASD, IDF, and AACE) recommend that when patients do not achieve glycemic goals with diet and lifestyle measures, diabetes care providers should start patients on metformin (unless contraindicated or not tolerated) either as monotherapy or in combination with other agents [4,10,11]. However, due in part to the progressive deterioration of β-cell function and declining endogenous insulin secretion, patients with type 2 diabetes will progressively need combination therapy with two or three oral agents to achieve optimal glycemic control. In this context, the incretin agents with their potential effects on β-cell function are widely used because their action to increase insulin secretion is glucose-dependent and thus does not carry an increased risk for hypoglycemia. Ultimately, many patients with type 2 diabetes will need

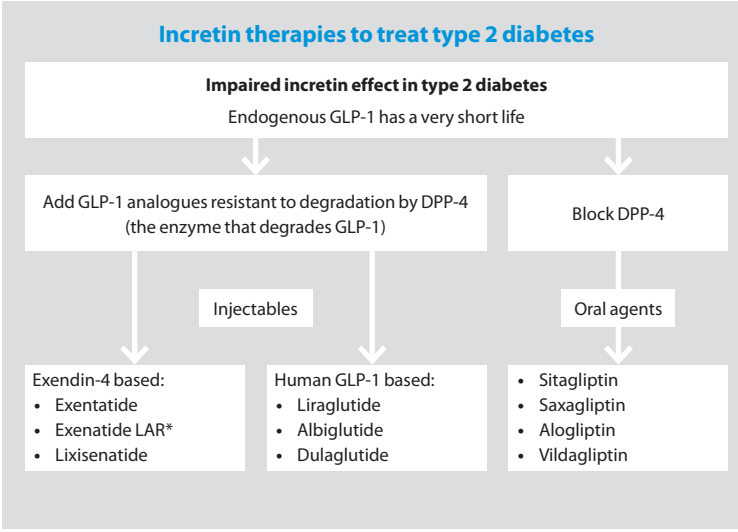

Figure 1.3 Rationale for incretin hormones to treat type 2 diabetes. *long-acting release. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

insulin to achieve optimal glycemic goals and incretin-based therapies can be used in combination with insulin.

More exciting, however, is the increasing recognition that the incretin agents have numerous extraglycemic effects that could translate into potential cardiovascular and other benefits. Long-term trials are in progress to document these effects. Recently the results of the long-term studies have been published and they have confirmed the long-term safety of the incretin agents. However, the studies (SAVOR-TIMI, EXAMINE, TECOS, and ELIXA) did not demonstrate any beneficial effects on cardiovascular events [13–16]. Also exciting is the development of technologies which permit the delivery of GLP-1 agents through an implantable subcutaneous pump delivery system such as the ITCA650 pump (Intacia Therapeutics, Boston, MA) that provides a slow and continuous subcutaneous delivery of exenatide for up to 1 year with a single implantation of a matchstick-like device. Oral GLP-1 agents are also in development.

In subsequent chapters in this handbook, the authors will expand on the rationale for the use of the incretin hormones as a target for therapy, characterize the clinical efficacy and benefits of GLP-1 agonists and DPP-4

Drug name	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin*
Usage and indications	Use with diet and exercise to improve glycemic control in Type 2 diabetes. Combination with sulfonylureas, metformin, pioglitazone, and insulin.				
Dosage and administration	Once daily with or without food	Once daily with or without food	Once daily with or without food	Once daily with or without food	Twice daily with or without food 50 mg QAM with SFUs
	25 mg (Cr Cl >50) 12.5 mg (Cr Cl <50) 6.25 mg (Cr Cl <30)	5 mg No dose adjustment for renal function	5 mg (Cr Cl >50) 2.5 mg (Cr Cl <50)	100 mg (Cr Cl >50) 50 mg (Cr Cl <50) 25 mg (Cr Cl >30)	50 mg BID (Cr Cl >50) 50 mg QD (Cr Cl <50)
Contraindication	Hypersensitivity	Hypersensitivity (ie urticaria, angioedema or bronchial hyperreactivity)	Hypersensitivity	Hypersensitivity (ie, anaphylaxis or angioedema)	Hypersensitivity
Warnings and precautions	When used with an SFU or insulin, a lower dose of SFU or insulin may be needed to reduce the risk of hypoglycemia. Post-marketing of pancreatitis (discontinue if suspicion of pancreatitis). Use with caution in patients with history of pancreatitis.				

Table 1.1 Comparison of dipeptidyl peptidase-4 (DPP-4) inhibitors. *Vildagliptin is not FDA approved. BID, twice a day; Cr Cl, creatinine clearance in ml/min; QAM, every day before noon; QD, once daily; SFU, sulfonylurea.

inhibitors, formulate treatment strategies with incretin-based therapy, and report on future and emerging therapies for treating type 2 diabetes.

References

1 Martin PMV, Martin-Granel E. 2,500-year evolution of the term epidemic. *Emerg Infect Dis*. 2006:12:976-980. wwwnc.cdc.gov/eid/article/12/6/pdfs/05-1263.pdf. Accessed January 5, 2015.

2 International Diabetes Federation. Diabetes: facts and figures. www.idf.org/worlddiabetesday/toolkit/gp/facts-figures. Accessed October 5, 2015.

3 DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58:773-795.

4 American Diabetes Association. Standards of medical care in diabetes 2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

5 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853.

6 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577-1589.

7 Duckworth W, Abraira C, Moritz T, et al; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360:129-139.

8 Patel A, MacMahon S, Chalmers J, et al. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560-2572.

9 Gerstein HC, Miller ME, Byington RP, et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545-2559.

10 International Diabetes Federation (IDF). IDF Clinical Guidelines: Global Guidelines for Type 2 Diabetes. 2011/2012. www.idf.org/guidelines. Accessed October 5, 2015.

11 Handelsman Y, Machanick JI, Blonde L, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan. AACE Diabetes Care Plan Guidelines. *Endocr Pract*. 2011;17(suppl 2):1-53. www.aace.com/files/dm-guidelines-ccp.pdf. Accessed October 5, 2015.

12 Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab*. 2013;17:819-837.

13 Scirica BM1, Bhatt DL, Braunwald E, et al. The design and rationale of the saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus-thrombolysis in myocardial infarction (SAVOR-TIMI) 53 study. *Am Heart J*. 2011;162:818-825.

14 White WB, Bakris GL, Bergenstal RM, et al. EXamination of cArdiovascular outcoMes with alogliptin versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. *Am Heart J*. 2011;162:620-626.

15 Green JB, Bethel MA, Paul SK, et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. *Am Heart J*. 2013;166:983-989.

16 Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide) (ELIXA). http://clinicaltrials.gov/ct2/show/NCT01147250. Accessed October 5, 2015.

Chapter 2

Incretin hormones as a target for therapy

Jens Juul Holst

Incretin hormone physiology

The incretin effect

Incretin hormones are responsible for the incretin effect, which is the amplification of insulin secretion when nutrients are taken in orally, as opposed to intravenously. Strictly speaking, the incretin effect refers to the intake of glucose. Oral administration of glucose appears to engage a mechanism that allows the body to secrete insulin more efficiently than intravenous glucose administration [1]. The mechanism involves an augmented insulin release that is usually three-fold more than that observed in response to intravenous glucose. These figures can be derived from actual measurements of insulin secretion rates based on C-peptide concentrations, deconvolution, and C-peptide elimination kinetics [2]. The augmented insulin secretion is caused by incretin hormones released from the gut in response to the oral intake of glucose such as glucose-dependent insulinotropic polypeptide (GIP; previously known as gastric inhibitory polypeptide) and glucagon-like peptide-1 (GLP-1). There may be more contributory peptides (eg, secretin and oxyntomodulin), but GIP and GLP-1 are likely the most important [3].

The incretin-producing cells

GIP and GLP-1 are peptide hormones produced by endocrine cells located in the intestinal mucosal epithelium. GIP is known to be produced in the so-called K cells, which may be found all over the small intestine, but have the highest density in the proximal part, including the duodenum.

S. Gough (ed.), *Handbook of Incretin-based Therapies in Type 2 Diabetes*, DOI 10.1007/978-3-319-08982-9_2

GLP-1 is produced in the L cells, which are found in all parts of the intestinal mucosa but with the highest densities in the ileum and the colon [4]. About 10–15% of the L cells express both GIP and GLP-1, but may also express other peptides including cholecystokinin (CCK), peptide YY (PYY), and neurotensin [5,6]. The nature of this apparent promiscuity is presently not clear but may have to do with the endocrine cell lifecycle, as the cells differentiate from the stem cell stage near the crypt villus transition, mature, move up the villus and, after just a few days, detach from the villus tip. Both L and K cells are open-type cells with a long cytoplasmic process reaching the gut lumen. The process is equipped with microvilli and it is thought that the cells may be able to sense nutrients because of the expression of molecular receptors and transporters in the microvillous cell membranes [7].

Incretin hormone biosynthesis and structure

GIP is formed from a precursor hormone, proGIP, from which the mature hormone, a 42-amino-acid peptide, is cleaved out by the enzyme prohormone convertase 1/3 [8,9]. GIP is released in response to nutrient ingestion, in particular glucose and lipids. The hormone binds to and activates a specific G protein-coupled receptor, the GIP-receptor [10]. Interestingly, the receptor is found in many tissues but more is known about its actions in the pancreatic islets and white adipose tissue [11]. In the pancreatic islets, the β cells, α cells, and somatostatin-producing δ cells all respond to GIP with stimulated secretion [12]. The mechanism involved is mainly activation of adenylate cyclase and accumulation of cyclic adenosine monophosphate (cAMP) [13].

GLP-1 is a product of the prohormone proglucagon, which is expressed in the pancreas, gut, and brainstem [14]. Phylogenetically, the L cells of the gut are related to pancreatic α cells. Both cells express the glucagon gene, which gives rise to the primary translation product proglucagon [15], but the common prohormone is differentially processed on the various tissues. In the α cells, proglucagon is cleaved by the enzyme prohormone convertase 2 (Figure 2.1). The products are:

- an N-terminal fragment (glicentin related pancreatic polypeptide [GRPP]);

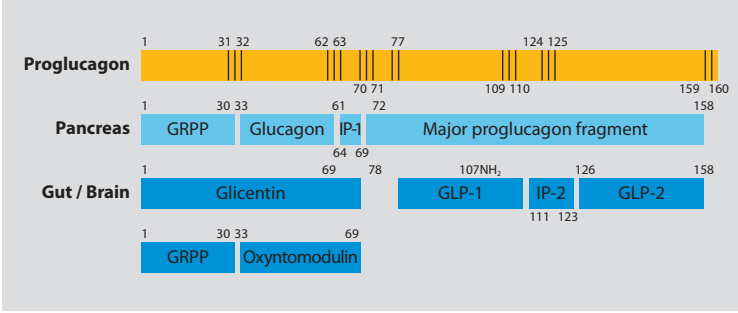

Figure 2.1 Processing of proglucagon. GLP, glucagon-like peptide; GRPP, glicentin-related pancreatic polypeptide; IP-1, intervening peptide-1; IP-2, intervening peptide 2.

- glucagon; and
- the so-called major proglucagon fragment (MPF), which contains two additional glucagon-like sequences: GLP-1 and 2 [16].

They are 'glucagon-like' due to an approximately 50% sequence homology with glucagon, but in the pancreas, they remain assembled in the major proglucagon fragment, which is probably biologically inactive.

In the gut, proglucagon is cleaved by another processing enzyme, prohormone convertase 1/3 [17]. Here, the products include glicentin, a large peptide in which the glucagon sequence is buried. Not much is known about its possible actions but it may be broken further down to oxyntomodulin, which contains the full glucagon sequence plus a C-terminal octapeptide and is highly bioactive [14] (Figure 2.1). It is called oxyntomodulin because it was thought to influence gastric acid secretion but it turns out to be an agonist for both the glucagon and the GLP-1 receptor and is thought to play a role in appetite regulation [18–20]. The two glucagon-like sequences are cleaved out of the major proglucagon fragment and are released to the circulation. GLP-1 is a 30-amino-acid peptide, while GLP-2 has 33 amino acids, but is not known to influence glucose metabolism or appetite [21–23].

GIP and GLP-1 action

GLP-1 acts on the pancreatic islets, where the β and δ cells express the specific GLP-1 receptor. In addition, GLP-1 has important actions on gastrointestinal secretion and motility (eg, delaying gastric emptying)

and acts to inhibit appetite and food intake [14]. The GLP-1 and GLP-2 are released after nutrient intake, including carbohydrates, lipids, and proteins. The most important actions of GIP are thought to occur in the pancreatic islets, peripheral adipose tissue, and bones.

Incretin secretion

For both of the incretin hormones, nutrient-induced secretion is thought to involve proteins expressed on the L and K cell membranes (Figure 2.2). For glucose, there is evidence for expression of sodium-glucose cotransporters 1 (SGLT1) in membranes of the apical process [24-26]. For every glucose molecule that enters the cell via SGLT1, two sodium molecules with positive charge also enter, causing depolarization. The depolarization, in turn, leads to opening of voltage-gated calcium channels allowing calcium to enter the cells, with ensuing exocytosis of the hormone-containing granules.

Fructose also stimulates secretion of GLP-1, but not GIP, in agreement with a demonstrated expression of GLUT-5 in the L cells [27]. Once in the cell, metabolism of fructose seems to be responsible for GLP-1 secretion.

Amino acids may also enter the cells in cotransport with sodium and may also be associated with depolarization and subsequent increase in intracellular calcium; however, a number of amino acids may also interact with G protein-coupled receptors on the cell surface, stimulating secretion [24]. Metabolism of the amino acids may also play a role; for instance glutamine, which is a preferred fuel for the small intestine, may be particularly effective [28]. The cells also express a number of lipid receptors, including the short-, medium-, and long-chain fatty acid receptors, which may activate specific intracellular pathways leading to secretion [29].

Like other small peptides, GIP and GLP-1 are eliminated in the kidneys by glomerular filtration, which would result in a half-life in the circulation of approximately 30 mins. However, both are eliminated much faster with (apparent) half-lives of less than 2 mins for GLP-1 and 7–8 min for GIP [30,31]. The immediate explanation for this is the actions of dipeptidyl peptidase-4 (DPP-4), an enzyme which cleaves off the two

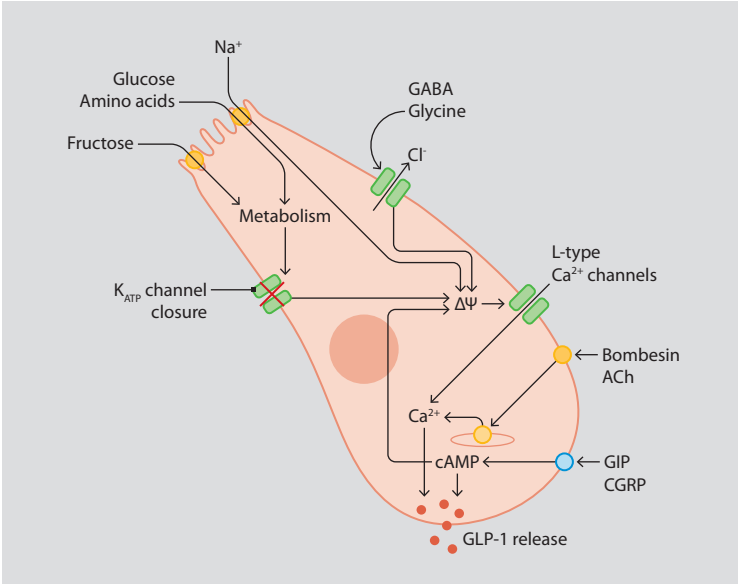

Figure 2.2 Potential pathways operating in L cells - identified in single cells. ACh, acetylcholine**;** ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CGRP, calcitonin gene related peptide; GABA, gamma-aminobutyric acid; GIP, gastric inhibitory polypeptide ; GLP-1, glucagon-like peptide-1.

N-terminal amino acids of the hormones and inactivates the molecules with respect to insulin secretion [32–34]

The degradation of GLP-1 by the DPP-4 system

The peptide is stored in and released from the L cells in the intact form and diffuses from the epithelium to the capillaries of the villi but as soon as it enters the blood vessels, it is degraded by DPP-4 expressed by the endothelial cells (Figure 2.3). In this way, only about one-third to one-quarter of what was released from the L cells leaves the gut intact [35]. GLP-1 then reaches the liver but another DPP-4 system is ready to degrade approximately half of what reaches the liver; only approximately 12% is left to reach the systemic circulation [36] and, here, circulating DPP-4 may destroy the rest [37]. In fact, it has recently been demonstrated in an animal model that only about 8% of the newly released GLP-1 may

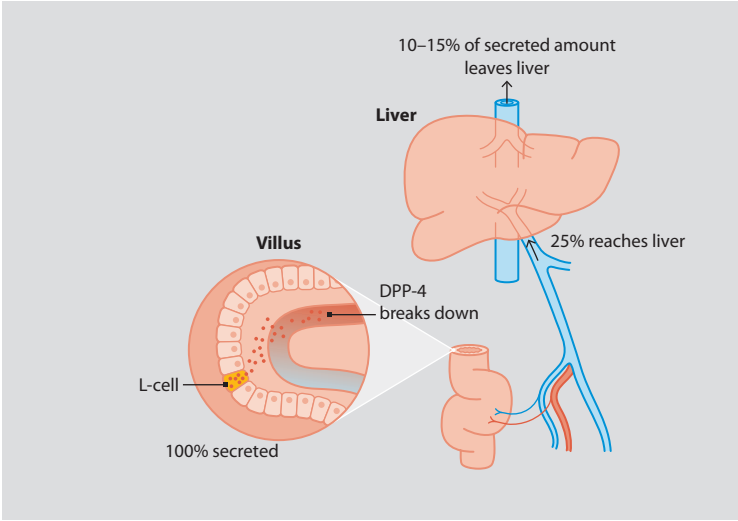

Figure 2.3 The degradation of GLP-1 by the DPP-4 system.

reach its peripheral targets with the arterial circulation [38]. It may seem paradoxical that a hormone is inactivated so rapidly and extensively after its release but the explanation seems to be that it is not acting only as a regular hormone via the circulation, but also interacts with afferent sensory nerve fibers in the gut [37].

The neural pathway

These nerve fibers signal to the brainstem and hypothalamus, where a reflex mechanism involving the efferent vagus regulates gastrointestinal motility and pancreatic secretion (Figure 2.4) [39,40]. Also, the appetite-regulating action of endogenous GLP-1 seems to involve the sensory vagal afferents [41], but high concentrations of active GLP-1 in plasma are also effective and may target GLP-1 receptors behind leaks in the blood–brain barrier (eg, in the postrema, subfornical organ, and median eminence). From here, GLP-1 may access the arcuate nucleus and reach appetite-regulating neurons, specifically the pro-opiomelanocortin (POMC)-expressing neurons, which express the GLP-1 receptor. This mechanism seems to be predominant for exogenous GLP-1 receptor agonists [42].

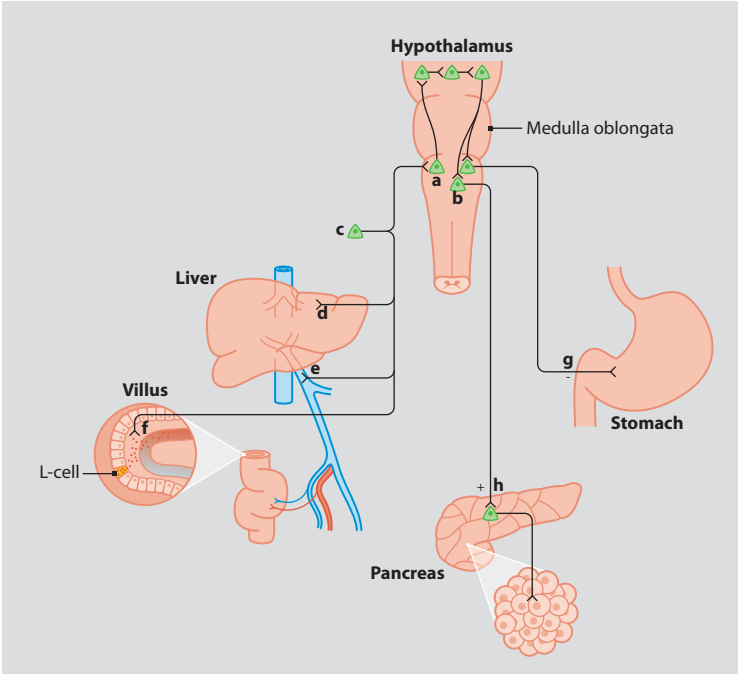

Figure 2.4 The neural pathway for GLP-1 action. GLP-1 secretion is stimulated by nutrients in the gut lumen (a magnified intestinal villus with an open-type L-cell is shown at the lower left), and newly released GLP-1 diffuses across the basal lamina into the lamina propria. On its way to the capillary, however, it may bind to and activate sensory afferent neurons (**f**) originating in the nodose ganglion (**c**), which may in turn activate neurons of the solitary tract nucleus (**a**). The same neuronal pathway may be activated by sensory neurons in the hepatoportal region (**e**) or in the liver tissue (**d**). Ascending fibers from the solitary tract neurons may generate reflexes in the hypothalamus, and descending impulses (from neurons in the paraventricular nucleus?) may activate vagal motor neurons (**b**), that send stimulatory (**h**) or inhibitory (**g**) impulses to the pancreas and the gastrointestinal tract. Interactions between ascending sensory nerve fibers and vagal motorneurons may also take place at the level of the brainstem.

For GIP, a similar mechanism cannot be demonstrated and, although GIP is also a substrate for DPP-4, local degradation by DPP-4 does not seem to be important and there is no evidence that GIP acts on its target receptors by any other route than via the bloodstream.

Measurement of the incretin hormones

The rapid degradation of the two peptides has important consequences when one has to decide which assay to use for determination of their

plasma concentration. Regarding intact GLP-1 (7–36) amide, its concentrations are often undetectable and the rise after stimulation is small, whereas the sum of the concentrations of the metabolite plus the intact hormone ('total-GLP-1') gives a better reflection of L-cell secretion and GLP-1 action [43,44]. This is because the metabolite is derived from GLP-1, which was once secreted from the villi in the intact form, and as such, had a chance to interact with vagal and intestinal sensory afferents before it entered the capillaries and got degraded [44]. In contrast, the concentration of the intact hormone only provides information about the very small fraction of intact GLP-1 which reaches a target (ie, islets) via the circulation and, as previously mentioned, this may be as little as 8% [38].

Incretin action in healthy individuals

The incretin function of GIP and GLP-1 in humans has been probed in mimicry studies where their meal responses in plasma were copied by intravenous infusions during glucose clamping [45]. These studies clearly demonstrated that the incretin actions of the two hormones are about equal and that they efficiently stimulate insulin secretion even at fasting glucose concentrations, and that the effects are greatly augmented by increases in plasma glucose concentration within the usual postprandial interval [45]. Glucagon secretion was also measured but, in this case, it turned out that GLP-1 markedly inhibited glucagon secretion on top of the inhibition cause by glucose, whereas GIP actually slightly increased glucagon secretion [45]. For GLP-1, the existence of an antagonist for the GLP-1 receptor, exendin-(9,39), has allowed a direct investigation of the relative importance of GLP-1 for insulin secretion induced by glucose, which in the study (see below) was instilled intraduodenally. Here, a significantly lower insulin response was obtained after antagonist treatment [46]. The antagonist also brought about an increased glucagon secretion, suggesting that GLP-1 is responsible for part of the inhibitory effect of oral glucose on glucagon secretion.

Incretin action in patients with type 2 diabetes

In patients with type 2 diabetes, the picture is strikingly different. As demonstrated in the now classic study by Nauck and colleagues, most

of the gastrointestinal amplification of insulin secretion is lost in these patients and is one of the major mechanisms behind their prandial glucose intolerance [47]. This is even more clearly illustrated by calculation of the gastrointestinally-mediated glucose disposal (GIGD), which relates the amount of intravenous glucose required to copy the oral glucose tolerance test (OGTT) to the oral dose [48,49]. Normally, this is about 25g for a 50g OGTT, meaning that 50% of the glucose is removed from the circulation by the gastrointestinal mechanism, but this figure may fall to 0% in patients with type 2 diabetes [50,51]. Importantly, neither the incretin effect nor GIGD are constant but vary with the amount of glucose administered. Thus, while non-diabetic individuals are able to increase their GIGD (and their incretin effect) by as much as 70–80% and keep their plasma excursions after oral glucose ingestion relatively constant regardless of the dose, patients with type 2 diabetes are unable to do so. This results in their plasma glucose excursions rising proportionally with the glucose load, eventually reaching very high levels [51].

The mechanism underlying the normal adaptation of the incretin effect and GIGD according to glucose dose is an increased incretin hormone secretion, resulting in proportionately increased insulin secretion. Both GIP and GLP-1 secretion is rapidly increased after glucose ingestion and may reach a maximal value after 30–45 minutes [51]. With a low dose, secretion rapidly declines thereafter; with higher doses, secretion is maintained at the initial level and continues for longer time, depending on the dose. A correlation of the responses with gastric emptying rates reveals the mechanism behind the graded hormone response: gastric emptying is progressively retarded by higher doses of glucose. In other words, it is the gastric emptying that regulates the entry of glucose into the small intestine so that glucose is emptied at a rather constant rate; with larger doses, the duration of the emptying phase is simply prolonged and, as a result, the incretin hormone secretion is also prolonged. Interestingly, these findings suggest that the gastric empting rate is one of the most important regulators of postprandial glucose profiles.

In the cited studies, there were no significant differences between the patients and the healthy controls regarding their GLP-1 and GIP responses to the varying doses of glucose, but this is not always the

case [50,51]. Obviously, one possible reason for the loss of the incretin effect in type 2 diabetes might be an impaired secretion of the two hormones. Indeed, a decreased GLP-1 response was reported in a large early study by Toft-Nielsen and colleagues, with similar findings made in several subsequent studies, particular with respect to the later phase of postprandial responses [52]; other, generally minor, studies have been unable to detect a significant differences, so the importance of an impaired GLP-1 response has been questioned [52,53].

However, for such comparisons, several important factors need to be considered. The most important is obesity, which is generally associated with impaired GLP-1 secretion for reasons that are unknown, but the impairment may be pronounced to the extent that a meal response may be missing altogether [54]. Secondly, as already alluded to, gastric emptying rates are extremely important for postprandial incretin responses, meaning that differences between controls and patients would have a major impact. In addition, differences in insulin sensitivity may play a role, and it has been demonstrated both directly and in meta-analyses that the severity and duration of diabetes influences secretion [55,56]. Finally, diabetes therapy may play a role. This is most importantly illustrated by metformin which stimulates GLP-1 secretion considerably, to an extent that increased GLP-1 secretion must be counted as one of the mechanisms whereby metformin lowers blood glucose in the patients [57]. In a recent large study of nearly 1500 individuals, it was clearly demonstrated that those with pre-diabetes or type 2 diabetes had 16–20% lower GLP-1 responses to an OGTT than people with a normal glucose test (NGT) [58]. Obese and overweight individuals had 25% and 15% lower GLP-1 responses, respectively, when compared to individuals with a normal weight, even after correction for age, sex, and glucose status. In addition, higher GLP-1 responses were associated with better insulin sensitivity and β-cell function and a lower degree of obesity. The conclusion, therefore, must be that an impaired secretion of GLP-1 is likely to contribute to the loss of the incretin effect in type 2 diabetes.

Therapeutic applications

Looking at the effects of GLP-1 and GIP, even more dramatic changes are seen. In one experiment, the hormones were infused into patients with poorly controlled type 2 diabetes during a hyperglycemic clamp (mainly established to ensure that all patients could be studied at the same clamp glucose level despite a wide range of fasting hyperglycemia levels), but neither the glucose clamp nor the hormone infusions had significant effects on insulin secretion, despite the same protocol having powerful effects on insulin secretion in healthy controls [59]. In further experiments, increasing the GIP infusion rate to supraphysiological levels did not help but actually stimulated glucagon secretion. On the other hand, increasing GLP-1 infusions to the therapeutic rate of 1.0–1.5 pmol/kg/min resulted in marked stimulation of insulin secretion, which reached similar levels as those seen in the controls during the same clamp conditions [60]. In addition, glucagon suppression in response to the glucose clamp, which was clearly impaired in the patients, was completely normalized. In other words, in these experiments, GLP-1 appeared to restore the sensitivity of both the β cells and the α cells to glucose [59,60].

Given the general lack of effect of GIP in type 2 diabetes, it seems unlikely that GIP will be useful in relation to diabetes therapy, although some GIP effects may be regained over time after improving glucose control with insulin or DPP-4 therapy. GLP-1, on the other hand, is extremely attractive due its apparent ability to restore the incretin effect in patients with diabetes [61,62]. This raises the question of whether the incretin defect in type 2 diabetes may also play a role in the development of type 2 diabetes. As discussed above, an impaired secretion of GLP-1 is an early observation but it is unlikely to play a causative role [54]. Rather, the loss is a consequence of the development of insulin resistance and glucose intolerance, as indicated from studies of incretin secretion and effects in experimentally induced insulin resistance [63] and in patients with secondary diabetes, (eg, following chronic pancreatitis), characterized by similar lack of effect of GIP and a preserved effect of high

concentrations of GLP-1 [64]. Therefore, one should not expect incretin-based therapies to be able to cause a full resolution of diabetes, although the power of GLP-1 may be sufficient to near normalize metabolism in some patients for a period of time [65].

The development of GLP-1 based therapies

GLP-1 receptor agonists

Turning GLP-1 into a clinically useful therapeutic agent was initially hampered by its extensive and immediate metabolism and although continuous subcutaneous infusion of GLP-1 with insulin pumps was demonstrated to dramatically improve metabolic control in patients with rather advanced disease [66], other approaches have been more successful (although, interestingly, one promising recent approach involves insertion into the subcutis of a small osmotic mini-pump, which is capable of delivering a stabilized GLP-1 receptor agonist for periods of 6–12 months) [67]. The remarkable and apparently unique sensitivity of GLP-1 towards the enzyme DPP-4 (even the closely homologous hormone GLP-2 is not degraded nearly as rapidly or extensively as GLP-1) soon gave inspiration to the development of analogs with substitutions of the second amino acid, which directs the proline-directed enzymes like DPP-4 [32, 68]. It turned out that several substituted analogs were both resistant and retained potency, but the problem with rapid renal elimination remained [68].

Two approaches were made to circumvent this problem. The first followed from the identification of a full and at least equipotent agonist for the GLP-1 receptor in the saliva of the lizard *Heloderma suspectum* (Gila monster) [69]. The molecule, exendin-4, is a 39-amino-acid peptide with 53% homology to GLP-1 in its first 30 amino acid sequence (although, it is not lizard's GLP-1; it has a sequence which more closely resembles GLP-1) and is resistant to DPP-4 but is not taken up by the kidneys and, thus, has an approximate 30-minute half-life in the circulation after intravenous administration [70,71]. This is sufficient to provide an exposure lasting for around 4–6 hours after a single subcutaneous injection, meaning that two daily injections might provide effective therapy.

The synthetic form, exenatide [72], shares most if not all of its actions with human GLP-1, including the effects on insulin and glucagon secretion,

gastric emptying, and appetite regulation, and has not generated any major surprises since its introduction in 2005. One might suspect that it would be antigenic, and indeed antibodies are formed in most patients, but the titers fall upon prolonged administration and are generally not associated with immunological problems or decreased efficacy [73]. Exenatide is also available in a slow-release formulation which provides very extended exposure and allows weekly administration [74].

Another approach has been to increase the dose in order to maintain adequate exposure for a longer period allowing once-daily dosing, and this turned out to be possible (lixisenatide) [75], although doses are limited by the gastrointestinal side effects shared by all GLP-1 receptor agonists (eg, nausea, vomiting). Another approach has been to associate the GLP-1 molecule with larger molecules, thereby avoiding both DPP-4-mediated degradation (presumably because of steric hindrance) and renal clearance. Examples are covalent or noncovalent associations of GLP-1 with albumin or antibody Fc-fragments.

The first of these molecules to reach the market was liraglutide, consisting of the normal mammalian GLP-1 sequence to which is attached a fatty acid (palmitic acid) which causes it to bind to albumin [76]. The molecule now behaves like a protein-bound hormone with a long half-life, escaping renal elimination and with a free fraction (1–2% of total) and with a diffusion potential similar to that of the parent molecule which is responsible for most of the actions. In other cases, the attachment has been covalent, and this is interesting because it raises the question of whether or not these analogs can access receptors 'behind' the filter of the capillary fenestrae in the islets and in the central nervous system [77]. The answer is that dulaglitide, a stabilized GLP-1 sequence covalently attached to an antibody Fc fragment, has nearly the same effect and side effect profile as liraglutide in spite of the difference in molecular size, but a much longer survival in the body, allowing weekly administration [78].

DPP-4 inhibitors

An entirely different approach consists of inhibiting the catalytic activity of the DPP-4 enzyme. Such inhibitors were originally developed for anti-immune therapies because DPP-4 is also expressed by certain cells of the

immune system, also known as CD26 [79]. However, very specific DPP-4 inhibitors turned out to have little or no effect on the immune system, so these projects were terminated. But when it was discovered that DPP-4 is responsible for the rapid degradation of GLP-1, it was also proposed that DPP-4 inhibitors could be used for diabetes therapy, analogous with the use of angiotensin-converting-enzyme (ACE) inhibitors for hypertension [80]. Subsequently, it was documented in animal models that a DPP-4 inhibitor available during GLP-1 degradation could enhance the survival of both endogenous and exogenous GLP-1 and result in much larger insulin responses [81]. This led to the development of new clinically useful DPP-4 inhibitors, the first of which was vildagliptin, as demonstrated in a clinical proof of concept study of patients with diabetes to lower HbA1c to a desired target of 7% over 52 weeks [82].

Subsequently, a large number of DPP-4 inhibitors have been developed and the first to reach the market was sitagliptin in 2006 [83]. The antidiabetic activity of the DPP-4 inhibitors is not quite as strong as that of the GLP-1 receptor agonists, but their great advantage is that they are orally available, most of them are suitable for once-daily administration, and that they have an extremely benign side effect profile, generally with frequencies similar to placebo. On the other hand, they have little effect on body weight. This may seem strange because they act by increasing the plasma concentrations of intact GIP and GLP-1, but the lack of an anorexic effect is most likely due to interference with the PYY system. The hormone PYY, co-stored with GLP-1 in many of the L cells, is also a substrate for DPP-4, converting it from PYY 1-36 to PYY 3-36. But PYY 1-36 is orexigenic and anorexigenic activity is gained only when it is converted to PYY 3-36 by DPP-4; this enables the molecule to interact with the Y-2 receptors which transmit appetite inhibitory effects in the hypothalamus. With the DPP-4 inhibitors, this conversion is prevented and so while the intact GLP-1 concentration is elevated, the PYY 3-36 concentration is simultaneously lowered, resulting in no or little net effect [84].

The antidiabetic action of DPP-4 inhibitors is consistent with their protective effect on GLP-1 and GIP, which both show significant and

approximate two- or three-fold elevations of their plasma concentrations of intact peptide [85]. The increase is somewhat lower than one would have expected from the concentration of the 'total hormones' as discussed above. There are probably two explanation for this: it turns out that the total hormone concentrations during therapy are generally lower than with placebo and these observations, with more direct measurements in experimental animal models [86,87], have suggested that the elevated concentrations of the intact hormones may feed back and inhibit the secretion of both GIP and GLP-1, perhaps by a mechanism involving local somatostatin secretion [88], thus limiting their secretion.

Another explanation is that degrading mechanisms other than DPP-4 (eg, neutral endopeptidase-22.11) may be involved in the degradation of at least GLP-1, which may reduce the concentration of the intact hormones relative to the concentration of total hormones [3,89]. Recently however, several groups have published studies of the incretin effect in humans, finding no difference between those treated with inhibitors and those treated with placebo [49,87,90]. This has generated theories of interference by the inhibitors with other systems unrelated to the incretins but with an effect on blood glucose.

Although this may be true (the list of potential substrates for DPP-4 is very long [32]), another explanation may be found in the proposed pathway of action for GLP-1 via the sensory afferents of the vagal system. As discussed above, this interaction takes place at a site (the lamina propria of the gut) where the hormone is still intact [37]; but if this is true, then DPP-4 inhibitors should not influence the interaction. Experiments to investigate this theory are currently ongoing.

Like GLP-1 receptor agonists, DPP-4 inhibitors are typically used on top of existing metformin therapy and in fixed combinations. The combination is associated with an apparently additive antihyperglycemic effect. This is important because metformin appears to enhance the secretion of GLP-1 [57]; in this way, one obtains an additional elevation of the intact GLP-1 concentrations and there is also experimental evidence that part of the antidiabetic action of metformin is exerted via stimulation of GLP-1 secretion.

References

1 Nauck MA, Homberger E, Siegel, et al. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab*. 1986;63:492-498.

2 Knop FK, Aaboe K, Vilsboll T, Madsbad S, Holst JJ, Krarup T. Reduced Incretin effect in obese subjecst with normal glucose tolerance as compared to lean control subjects. *Diabetes*. 2008; 57[supplement 1]:A410.

3 Hansotia T, Baggio LL, Delmeire D, et al. Double incretin receptor knockout (DIRKO) mice reveal an essential role for the enteroinsular axis in transducing the glucoregulatory actions of DPP-IV inhibitors. *Diabetes*. 2004;53:1326-1335.

4 Kuhre RE, Albrechtsen NW, Windelov JA, Svendsen B, Hartmann B, Holst JJ. GLP-1 amidation efficiency along the length of the intestine in mice, rats and pigs and in GLP-1 secreting cell lines. *Peptides*. 2014;55:52-7.

5 Svendsen B, Pedersen J, Jacob Wewer AN, et al. An analysis of co-secretion and co-expression of gut hormones from male rat proximal and distal small intestine. *Endocrinology*. 2015;156:847-857.

6 Egerod KL, Engelstoft MS, Grunddal KV, Nohr MK, Secher A, Sakata I, et al. A Major Lineage of Enteroendocrine Cells Coexpress CCK, Secretin, GIP, GLP-1, PYY, and Neurotensin but Not Somatostatin. *Endocrinology*. 2012;153:5782-5795.

7 Gribble FM. The gut endocrine system as a coordinator of postprandial nutrient homoeostasis. *Proc Nutr Soc*. 2012;1-7.

8 Takeda J, Seino Y, Tanaka K, et al. Sequence of an intestinal cDNA encoding human gastric inhibitory polypeptide precursor. *Proc Natl Acad Sci U S A*. 1987;84:7005-7008.

9 Ugleholdt R, Poulsen ML, Holst PJ, et al. Prohormone convertase 1/3 is essential for processing of the glucose-dependent insulinotropic polypeptide precursor. *J Biol Chem*. 2006;281:11050-11057.

10 Volz A, Goke R, Lankat Buttgereit B, Fehmann HC, Bode HP, Goke B. Molecular cloning, functional expression, and signal transduction of the GIP-receptor cloned from a human insulinoma. *FEBS Lett*. 1995;373:23-29.

11 Miyawaki K, Yamada Y, Ban N, et al. Inhibition of gastric inhibitory polypeptide signaling prevents obesity. *Nat Med*. 2002;8:738-742.

12 de HJ, Rasmussen C, Coy DH, Holst JJ. Glucagon-like peptide-1, but not glucose-dependent insulinotropic peptide, inhibits glucagon secretion via somatostatin (receptor subtype 2) in the perfused rat pancreas. *Diabetologia*. 2008;51:2263-2270.

13 Drucker DJ. The biology of incretin hormones. *Cell Metab*. 2006;3:153-165.

14 Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev*. 2007;87:1409-1439.

15 Bell GI, Santerre RF, Mullenbach GT. Hamster preproglucagon contains the sequence of glucagon and two related peptides. *Nature*. 1983;302:716-718.

16 Holst JJ, Bersani M, Johnsen AH, Kofod H, Hartmann B, Orskov C. Proglucagon processing in porcine and human pancreas. *J Biol Chem*. 1994;269:18827-18833.

17 Rouille Y, Martin S, Steiner DF. Differential processing of proglucagon by the subtilisin-like prohormone convertases PC2 and PC3 to generate either glucagon or glucagon-like peptide. *J Biol Chem*. 1995;270:26488-26496.

18 Bataille D, Blache P, Bergeron F. Endoprotease regulation of miniglucagon production. *Ann N Y Acad Sci. 1996*;805:1-8;Disc. 8-9.

19 Baldissera FG, Holst JJ, Knuhtsen S, Hilsted L, Nielsen OV. Oxyntomodulin (glicentin-(33-69)): pharmacokinetics, binding to liver cell membranes, effects on isolated perfused pig pancreas, and secretion from isolated perfused lower small intestine of pigs. *Regul Pept*. 1988;21:151-166.

20 Cohen MA, Ellis SM, Le Roux CW, et al. Oxyntomodulin suppresses appetite and reduces food intake in humans. *J Clin Endocrinol Metab*. 2003;88:4696-46701.

21 Orskov C, Bersani M, Johnsen AH, Hojrup P, Holst JJ. Complete sequences of glucagon-like peptide-1 from human and pig small intestine. *J Biol Chem*. 1989;264:12826-12829.

22 Buhl T, Thim L, Kofod H, Orskov C, Harling H, Holst JJ. Naturally occurring products of proglucagon 111-160 in the porcine and human small intestine. *J Biol Chem*. 1988;263:8621-8624.

23 Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. *Gut*. 2011;60:902-914.

24 Parker HE, Reimann F, Gribble FM. Molecular mechanisms underlying nutrient-stimulated incretin secretion. *Expert Rev Mol Med*. 2010;12:e1.

25 Kuhre RE, Frost CR, Svendsen B, Holst JJ. Molecular Mechanisms of Glucose-Stimulated GLP-1 Secretion From Perfused Rat Small Intestine. *Diabetes*. 2015;64:370-382.

26 Parker HE, Habib AM, Rogers GJ, Gribble FM, Reimann F. Nutrient-dependent secretion of glucose-dependent insulinotropic polypeptide from primary murine K cells. *Diabetologia*. 2009;52:289-298.

27 Kuhre RE, Frost CR, Svendsen B, Holst JJ. Molecular mechnisms of glucose-stimulated GLP-1 secretion from perfused rat small intestine. *Diabetes*. 2015; 64:370-382.

28 Tolhurst G, Reimann F, Gribble FM. Nutritional regulation of glucagon-like peptide-1 secretion. *J Physiol*. 2009;587(Pt 1):27-32.

29 Hansen HS, Rosenkilde MM, Holst JJ, Schwartz TW. GPR119 as a fat sensor. *Trends Pharmacol Sci*. 2012;33:374-381.

30 Vilsboll T, Agerso H, Krarup T, Holst JJ. Similar elimination rates of glucagon-like peptide-1 in obese type 2 diabetic patients and healthy subjects. *J Clin Endocrinol Metab*. 2003;88:220-224.

31 Vilsboll T, Agerso H, Lauritsen T, et al. The elimination rates of intact GIP as well as its primary metabolite, GIP 3-42, are similar in type 2 diabetic patients and healthy subjects. *Regul Pept*. 2006;137:168-172.

32 Mentlein R. Dipeptidyl-peptidase IV (CD26)--role in the inactivation of regulatory peptides. *Regul Pept*. 1999;85:9-24.

33 Deacon CF, Johnsen AH, Holst JJ. Degradation of glucagon-like peptide-1 by human plasma in vitro yields an N-terminally truncated peptide that is a major endogenous metabolite in vivo. *J Clin Endocrinol Metab*. 1995;80:952-957.

34 Deacon CF, Nauck MA, Meier J, Hucking K, Holst JJ. Degradation of endogenous and exogenous gastric inhibitory polypeptide in healthy and in type 2 diabetic subjects as revealed using a new assay for the intact peptide. *J Clin Endocrinol Metab*. 2000;85:3575-3581.

35 Hansen L, Deacon CF, Orskov C, Holst JJ. Glucagon-like peptide-1-(7-36)amide is transformed to glucagon-like peptide-1-(9-36)amide by dipeptidyl peptidase IV in the capillaries supplying the L cells of the porcine intestine [In Process Citation]. *Endocrinology*. 1999;140:5356-5363.

36 Deacon CF, Pridal L, Klarskov L, Olesen M, Holst JJ. Glucagon-like peptide 1 undergoes differential tissue-specific metabolism in the anesthetized pig. *Am J Physiol*. 1996;271(3 Pt 1):E458-E464.

37 Holst JJ, Deacon CF. Glucagon-like peptide-1 mediates the therapeutic actions of DPP-IV inhibitors. *Diabetologia*. 2005;48:612-615.

38 Hjøllund KR, Deacon CF, Holst JJ. Dipeptidyl peptidase-4 inhibition increases portal concentrations of intact glucagon-like peptide-1 (GLP-1) to a greater extent than peripheral concentrations in anaesthetised pigs. *Diabetologia*. 2011;54:2206-2208.

39 Imeryuz N, Yegen BC, Bozkurt A, Coskun T, Villanueva-Penacarrillo ML, Ulusoy NB. Glucagon-like peptide-1 inhibits gastric emptying via vagal afferent- mediated central mechanisms. *Am J Physiol*. 1997;273(4 Pt 1):G920-G927.

40 Wettergren A, Wojdemann M, Holst JJ. Glucagon-like peptide-1 inhibits gastropancreatic function by inhibiting central parasympathetic outflow. *Am J Physiol*. 1998;275(5 Pt 1):G984-G992.

41 Ruttimann EB, Arnold M, Hillebrand JJ, Geary N, Langhans W. Intrameal hepatic portal and intraperitoneal infusions of glucagon-like peptide-1 reduce spontaneous meal size in the rat via different mechanisms. *Endocrinology*. 2009;150:1174-1181.

42 Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest*. 2014;124:4473-4488.

43 Bak MJ, Wewer Albrechtsen NJ, Pedersen J, et al. Specificity and sensitivity of commercially available assays for glucagon-like peptide-1 (GLP-1): implications for GLP-1 measurements in clinical studies. *Diabetes Obes Metab*. 2014;16:1155-1164.
44 Deacon CF, Holst JJ. Immunoassays for the incretin hormones GIP and GLP-1. *Best Pract Res Clin Endocrinol Metab*. 2009;23:425-432.
45 Vilsboll T, Krarup T, Madsbad S, Holst JJ. Both GLP-1 and GIP are insulinotropic at basal and postprandial glucose levels and contribute nearly equally to the incretin effect of a meal in healthy subjects. *Regul Pept*. 2003;114:115-121.
46 Salehi M, Vahl TP, D'Alessio DA. Regulation of islet hormone release and gastric emptying by endogenous glucagon-like peptide 1 after glucose ingestion. *J Clin Endocrinol Metab*. 2008;93:4909-4916.
47 Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia*. 1986;29:46-52.
48 Knop FK, Aaboe K, Vilsboll T, Madsbad S, Krarup T, Holst JJ. Reduced incretin effect in obese subjects with normal glucose tolerance as compared to lean control subjects. *Diabetologia*.2010;51(suppl 1):S258.
49 Rhee NA, Ostoft SH, Holst JJ, Deacon CF, Vilsboll T, Knop FK. The impact of dipeptidyl peptidase 4 inhibition on incretin effect, glucose tolerance, and gastrointestinal-mediated glucose disposal in healthy subjects. *Eur J Endocrinol*. 2014;171:353-362.
50 Nauck MA, Homberger E, Siegel EG, et al. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab*. 1986;63:492-498.
51 Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsboll T. Impaired regulation of the incretin effect in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2011;96:737-745.
52 Toft-Nielsen MB, Damholt MB, Madsbad S, et al. Determinants of the impaired secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetic patients. *J Clin Endocrinol Metab*. 2001; 86:3717-3723.
53 Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ. Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? *Diabetologia*. 2011;54:10-18.
54 Holst JJ, Knop FK, Vilsboll T, Krarup T, Madsbad S. Loss of incretin effect is a specific, important, and early characteristic of type 2 diabetes. *Diabetes Care*. 2011;34 (suppl 2):S251-S257.
55 Rask E, Olsson T, Soderberg S, Johnson O, Seckl J, Holst JJ, et al. Impaired incretin response after a mixed meal is associated with insulin resistance in nondiabetic men. *Diabetes Care*. 2001;24:1640-1645.
56 Calanna S, Christensen M, Holst JJ, et al. Secretion of glucagon-like peptide-1 in patients with type 2 diabetes mellitus: systematic review and meta-analyses of clinical studies. *Diabetologia*. 2013;56:965-972.
57 Migoya EM, Miller J, Larson P, et al. Sitagliptin, a selective DPP-4 inhibitor, and metformin have complementary effects to increase active FGLP-1 concentrations. *Diabetes*. 2007; 56(suppl 1):A74.
58 Faerch K, Torekov SS, Vistisen D, et al. Glucagon-like peptide-1 (GLP-1) response to oral glucose is reduced in pre-diabetes, screen-detected type 2 diabetes and obesity, and influenced by sex: The ADDITION-PRO Study. *Diabetes*. 2015;64:2513-2525.
59 Hojberg PV, Vilsboll T, Rabol R, et al. Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. *Diabetologia*. 2009;52:199-207.
60 Vilsboll T, Krarup T, Madsbad S, Holst JJ. Defective amplification of the late phase insulin response to glucose by GIP in obese Type II diabetic patients. *Diabetologia*. 2002;45:1111-1119.
61 Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon- like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia*. 1993;36:741-744.

62 Rachman J, Barrow BA, Levy JC, Turner RC. Near-normalisation of diurnal glucose concentrations by continuous administration of glucagon-like peptide-1 (GLP-1) in subjects with NIDDM. *Diabetologia*. 1997;40:205-211.
63 Jensen DH, Aaboe K, Henriksen JE, et al. Steroid-induced insulin resistance and impaired glucose tolerance are both associated with a progressive decline of incretin effect in first-degree relatives of patients with type 2 diabetes. *Diabetologia*. 2012;55:1406-1416.
64 Vilsboll T, Knop FK, Krarup T, et al. The pathophysiology of diabetes involves a defective amplification of the late-phase insulin response to glucose by glucose-dependent insulinotropic polypeptide-regardless of etiology and phenotype. *J Clin Endocrinol Metab*. 2003;88:4897-4903.
65 Toft-Nielsen MB, Madsbad S, Holst JJ. Determinants of the effectiveness of glucagon-like peptide-1 in type 2 diabetes. *J Clin Endocrinol Metab*. 2001;86:3853-3860.
66 Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet*. 2002;359:824-830.
67 Henry RR, Rosenstock J, Logan D, Alessi T, Luskey K, Baron MA. Continuous subcutaneous delivery of exenatide via ITCA 650 leads to sustained glycemic control and weight loss for 48 weeks in metformin-treated subjects with type 2 diabetes. *J Diabetes Complications*. 2014;28:393-398.
68 Deacon CF, Knudsen LB, Madsen K, Wiberg FC, Jacobsen O, Holst JJ. Dipeptidyl peptidase IV resistant analogues of glucagon-like peptide-1 which have extended metabolic stability and improved biological activity. *Diabetologia*. 1998;41:271-278.
69 Raufman JP, Singh L, Singh G, Eng J. Truncated glucagon-like peptide-1 interacts with exendin receptors on dispersed acini from guinea pig pancreas. Identification of a mammalian analogue of the reptilian peptide exendin-4. *J Biol Chem*. 1992;267:21432-21437.
70 Chen YE, Drucker DJ. Tissue-specific expression of unique mRNAs that encode proglucagon-derived peptides or exendin 4 in the lizard. *J Biol Chem*. 1997;272:4108-4115.
71 Edwards CM, Stanley SA, Davis R, et al. Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol Endocrinol Metab*. 2001;281:E155-E161.
72 Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin*. 2008;24:275-286.
73 Fineman MS, Mace KF, Diamant M, et al. Clinical relevance of anti-exenatide antibodies: safety, efficacy and cross-reactivity with long-term treatment. *Diabetes Obes Metab*. 2012;14:546-554.
74 Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet*. 2008;372:1240-1250.
75 Schmidt LJ, Habacher W, Augustin T, Krahulec E, Semlitsch T. A systematic review and meta-analysis of the efficacy of lixisenatide in the treatment of patients with type 2 diabetes. *Diabetes Obes Metab*. 2014;16:769-779.
76 Gough SC. Liraglutide: from clinical trials to clinical practice. *Diabetes Obes Metab*. 2012;14(suppl 2):33-40.
77 Baggio LL, Huang Q, Brown TJ, Drucker DJ. A recombinant human glucagon-like peptide (GLP)-1-albumin protein (albugon) mimics peptidergic activation of GLP-1 receptor-dependent pathways coupled with satiety, gastrointestinal motility, and glucose homeostasis. *Diabetes*. 2004;53:2492-2500.
78 Thompson AM, Trujillo JM. Dulaglutide: The newest GLP-1 receptor agonist for the management of type 2 diabetes. *Ann Pharmacother*. 2015 Jan 6.
79 Marguet D, Baggio L, Kobayashi T, et al. Enhanced insulin secretion and improved glucose tolerance in mice lacking CD26. *Proc Natl Acad Sci U S A*. 2000;97:6874-6879.

80 Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Holst JJ. Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects. *Diabetes*. 1995;44:1126-1131.

81 Deacon CF, Hughes TE, Holst JJ. Dipeptidyl peptidase IV inhibition potentiates the insulinotropic effect of glucagon-like peptide 1 in the anesthetized pig. *Diabetes*. 1998;47:764-769.

82 Ahren B, Gomis R, Standl E, Mills D, Schweizer A. Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2004;27:2874-2880.

83 Deacon CF, Holst JJ. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes: comparison, efficacy and safety. *Expert Opin Pharmacother*. 2013;14:2047-2058.

84 Aaboe K, Knop FK, Vilsboll T, et al. Twelve weeks treatment with the DPP-4 inhibitor, sitagliptin, prevents degradation of peptide YY and improves glucose and non-glucose induced insulin secretion in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2010;12:323-333.

85 Mari A, Sallas WM, He YL, et al. Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed {beta}-cell function in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2005;90:4888-4894.

86 Deacon CF, Wamberg S, Bie P, Hughes TE, Holst JJ. Preservation of active incretin hormones by inhibition of dipeptidyl peptidase IV suppresses meal-induced incretin secretion in dogs. *J Endocrinol.* 2002;172:355-362.

87 Vardarli I, Arndt E, Deacon CF, Holst JJ, Nauck MA. Effects of sitagliptin and metformin treatment on incretin hormone and insulin secretory responses to oral and "isoglycemic" intravenous glucose. *Diabetes*. 2014;63:663-674.

88 Hansen L, Hartmann B, Bisgaard T, Mineo H, Jørgensen PN, Holst JJ. Somatostatin restrains the secretion of glucagon-like peptide-1 and 2 from isolated perfused porcine ileum. *Am J Physiol*. 2000;278:E1010-E1018.

89 Trebbien R, Klarskov L, Olesen M, Holst JJ, Carr RD, Deacon CF. Neutral endopeptidase 24.11 is important for the degradation of both endogenous and exogenous glucagon in anesthetized pigs. *Am J Physiol Endocrinol Metab*. 2004;287:E431-E438.

90 Muscelli E, Casolaro A, Gastaldelli A, Mari A, Seghieri G, Astiarraga B, et al. Mechanisms for the antihyperglycemic effect of sitagliptin in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2012;97:2818-2826.

Chapter 3

Glucagon-like peptide-1 receptor agonists

Baptist Gallwitz

Introduction

Native glucagon-like peptide-1 (GLP-1) is not practical for therapeutic use due to a short half-life caused by ubiquitous, fast, and effective in vivo degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). The physiological and pharmacological actions of GLP-1 were used to develop two drug classes of incretin-based therapies: GLP-1 receptor agonists (GLP-1 RA) for injectable therapy and orally active DPP-4 inhibitors. GLP-1 RA stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner. They also have extrapancreatic effects; the most important for type 2 diabetes therapy are the slowing of gastric emptying, a stimulation of sensations of satiety and fullness by direct action on the central nervous system, and body weight reduction [1].

The class of GLP-1 RA can be divided into human GLP-1 analogs with a longer biological half-life than native GLP-1 and peptides with a high amino acid sequence similarity to human GLP-1 that are able to bind and to activate the GLP-1 receptor [2]. The latter ones are derived from the structure of the reptilian peptide exendin-4 that is a DPP-4-resistant GLP-1 RA. Besides this distinction regarding the structure, GLP-1 RAs can be classified according to their durability of action as short-acting (once- or twice-daily injection) and long-acting (once-weekly injection) [3,4]. The long-acting GLP-1 RAs activate the GLP-1 receptor continuously in contrast to the short-acting ones. The pharmacokinetic differences between these drugs lead to important differences in their

S. Gough (ed.), *Handbook of Incretin-based Therapies in Type 2 Diabetes*, DOI 10.1007/978-3-319-08982-9_3

pharmacodynamic profiles. The short-acting GLP-1 RAs predominantly lower the postprandial plasma glucose through inhibition of gastric emptying, whereas the long-acting compounds have a stronger effect on fasting glucose concentrations, which is mediated mainly through their insulinotropic and glucagonostatic actions.

The adverse effect profiles of these compounds also differ. The individual properties of the various GLP-1 RAs might enable incretin-based treatment of type 2 diabetes mellitus to be tailored to the needs of each patient [4]. Figure 3.1 shows the general classification of GLP-1 RAs.

GLP-1 receptor agonists

Exenatide

Exenatide was the first GLP-1 RA for the treatment of type 2 diabetes introduced in 2006. Exenatide is the synthetic form of exendin-4 that was discovered in the saliva of the Gila monster (*Heloderma suspectum*) in 1992. Exenatide has a 53% amino acid sequence similarity to human GLP-1 and the biological half-time of 3.5 hours after injection makes it suitable for twice-daily injection. It is mostly used in combination with metformin and/or a sulfonylurea or basal insulin in patients failing to reach therapeutic goals with monotherapy [2,4–6]. In its rapid-acting form, it is injected subcutaneously twice-daily. Clinical studies have

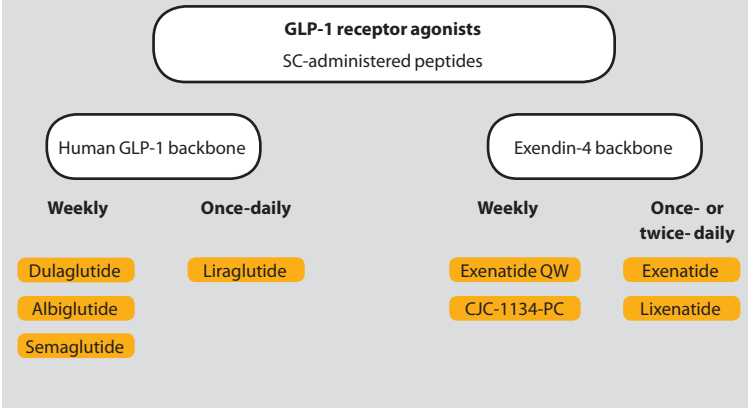

Figure 3.1 Classification of glucagon-like peptide (GLP)-1 receptor agonists. QW, once-weekly; SC, subcutaneous.

demonstrated a sustained HbA1c reduction of approximately 1% and a decrease in body weight of 2.5–4.5 kg, depending on the study [2,4,6,7]. In a long-term study with >4 years observation time, exenatide was superior to glimepiride regarding its efficacy and durability in lowering the HbA1c in patients with metformin failure [6]. Fewer patients in the exenatide group required rescue medication and the incidence of hypoglycemia was significantly lower than in the glimepiride cohort [6].

A slow-release formulation for once-weekly administration was introduced in 2012, mainly for the use in patients failing to reach treatment targets with metformin or an oral drug combination [4,7,8]. In this formulation, exenatide is embedded in a suspension of slow-release microspheres. The once-weekly preparation showed a higher efficacy in lowering HbA1c and fasting plasma glucose than twice-daily exenatide in a direct comparison [9,10]. On the other hand, twice-daily exenatide had a stronger effect in lowering postprandial glucose due to the differential effect of gastric emptying (Figure 3.2) [4]. Because exenatide is a non-human peptide, antibody formation is observed in approximately 40% of patients under therapy [7,11]. However, there seems to be little clinical significance because the antibodies do not lead to a reduction of efficacy or other clinical effects. Also, they do not cross-react with native human GLP-1 and the titers disappear after cessation of treatment [12].

Liraglutide

Liraglutide is the first human GLP-1 RA with two modifications in the amino acid sequence of native human GLP-1 and an attachment of a fatty acid side chain to the peptide. With a biological half-time of approximately 13.5 hours it is suitable for once-daily subcutaneous injections [2,4,13]. In clinical studies in patients with type 2 diabetes, liraglutide was efficacious and safe across all stages of the natural course of type 2 diabetes, in monotherapy, as well as in combination with either one or more oral antidiabetic agents as well as with basal insulin. Liraglutide given once-daily at doses of either 1.2 mg or 1.8 mg effectively lowered HbA1c in various combinations with oral antidiabetic drugs by approximately 1.0–1.5%. It also caused a significant weight loss comparable to that observed in studies with exenatide and other GLP-1 RAs. As in other studies with

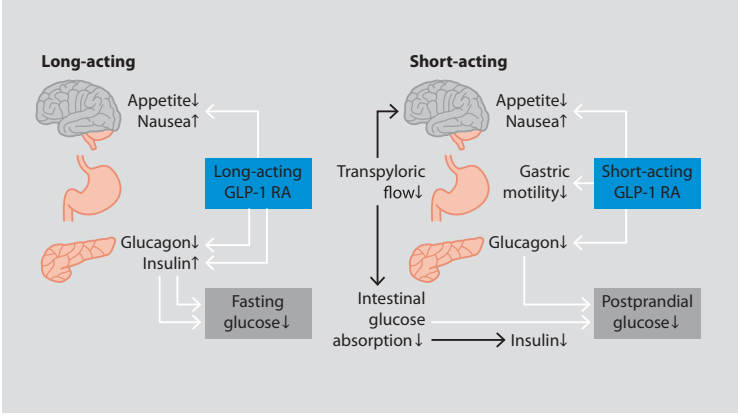

Figure 3.2 Differential action of short- and long acting glucagon-like peptide-1 receptor agonists (GLP-1 RA) explaining their different action on fasting- and postprandial glucose. Adapted with permission from Meier [4] ©Nature.

GLP-1 RA, hypoglycemia incidence rates were comparable to placebo in the liraglutide studies, provided no sulfonylurea was used in the combination with liraglutide. Gastrointestinal side effects were also common in the clinical studies with liraglutide; however, in a direct head-to-head study with exenatide [14], nausea and vomiting were less frequent with liraglutide and present for a shorter period at the beginning of therapy.

In clinical studies, antibodies against liraglutide were detected in approximately 8–9% of patients [2,4,13]. Liraglutide was superior to exenatide regarding lowering the glycemic parameters (glycated hemoglobin; HbA1c), fasting glucose, and improving homeostatic model assessment of β cells (HOMA-B) in a direct head-to-head study [6]. Liraglutide improved the first phase of insulin secretion after intravenous glucose, as well as the insulin response to a maximal stimulation with arginine. Mild-to-moderate renal impairment did not alter the pharmacokinetic profile of liraglutide [2,4]. In a direct head-to-head comparison with the DPP-4 inhibitor sitagliptin, liraglutide was superior in lowering glycemic parameters and body weight in two doses (1.2 mg and 1.8 mg) given once daily [15].

Lixisenatide

Lixisenatide is a 44-amino-acid peptide based on exendin-4, which differs in structure through the deletion of a proline residue and the addition of six lysine residues at the C terminus. It is a once-daily prandial GLP-1 receptor agonist that is administered 20 μg once-daily via subcutaneous injection. The biological half-life is approximately 3.5 hours. In an early clinical trial, there was no significant difference in efficacy found between once- or twice-daily dosing and, thus, a once-daily dose is recommended in use for clinical practice [16]. The efficacy, safety, and tolerability of lixisenatide once-daily was examined in monotherapy, with oral antidiabetic agents (metformin, sulfonylureas, or thiazolidinediones), or basal insulin glargine [17,18].

Additionally two studies compared lixisenatide directly with exenatide [19] and liraglutide [20]. In these studies, lixisenatide was non-inferior to exenatide and liraglutide regarding glycemic effects and body weight loss [19,20]. The side effect profile, especially concerning gastrointestinal side effects, is comparable to the other GLP-1 RAs. The clinical studies with lixisenatide demonstrate that lixisenatide given once daily effectively lowers blood glucose levels, predominantly by reducing postprandial plasma glucose [17,18]. The postprandial effect of lixisenatide is predominantly pronounced for the first meal following injection [16,20].

Albiglutide

Albiglutide is a long-acting GLP-1 RA consisting of two copies of a 30-amino-acid sequence of a human GLP-1 dimer genetically fused to human albumin. Resistance to DPP-4 degradation is achieved by a single amino acid substitution (glycine to alanine) at the eighth position. The fusion to albumin and the amino acid substitution both result in a longer half-life and, thus, the need for less-frequent dosing. Albiglutide has a molecular weight of approximately 70,000 g/mol. Maximum concentrations of albiglutide were reached 3–5 days after a single 30 mg subcutaneous dose. Steady-state concentrations are achieved after 4–5 weeks of once-weekly administration. The elimination half-life is approximately 5–7 days, making it suitable for once-weekly administration [21].

Albiglutide has been studied as monotherapy and add-on therapy to metformin, sulfonylureas, thiazolidinediones, insulin glargine, and

varying combinations of these agents [22–27]. Clinical studies have shown albiglutide to be superior to placebo [22], sitagliptin [25], and glimepiride [25], and noninferior to insulin glargine and insulin lispro at reducing HbA1c, with changes from baseline ranging from −0.55% to −0.9% [23,26]. Noninferiority was not achieved when compared to liraglutide and pioglitazone. Weight changes ranged from +0.28 to −1.21 kg. The most common side effects are gastrointestinal and injection-site reactions. Advantages include once-weekly dosing and fewer gastrointestinal side effects when compared with liraglutide, but it is less effective at reducing HbA1c and weight [27]. To date, it has not been compared head-to-head with other GLP-1 RAs [21].

Dulaglutide

Dulaglutide, a human GLP-1 RA with once-daily dosing, has recently been approved for use in Europe, Japan, and the United States. It is a GLP-1 peptide fused to immunoglobulin G (IgG) that exhibits extended biological activity due to its increased half-life (~90 hours), compared with native GLP-1, supporting once-weekly administration of this drug [28]. Doses of 0.05–8.0 mg per week have resulted in HbA1c level reductions of 0.2–1.2% after 5 weeks [29]. Significant mean reductions in body weight comparable to those observed with liraglutide were observed in the Phase III trials with 0.75 mg and 1.5 mg doses of dulaglutide. In one clinical study, the add-on of dulaglutide to patients failing on metformin was noninferior compared to the addition of insulin glargine at the 0.75 mg dose and superior at the 1.5 mg dose [30]. A direct head-to-head study comparing liraglutide (1.8 mg) with dulaglutide (1.5 mg) demonstrated noninferiority for dulaglutide regarding the reduction of HbA1c and body weight [31,32].

Semaglutide

Semaglutide is another once-weekly GLP-1 RA with a fatty acid side-chain covalently bound to the altered human GLP-1 peptide sequence to prolong the biological half-life and to prevent degradation by DPP-4. Semaglutide is presently in Phase III clinical trials; first data shows a dose-dependent reduction in HbA1c and body weight characteristic for

a GLP-1 RA with promising efficacy [33]. An oral form of semaglutide is also in the early stages of development.

GLP-1 RA/basal insulin combination solutions

IDegLira is the first fixed combination of a GLP-1 RA (liraglutide) with basal insulin (insulin degludec) in one solution. The mixture contains 1.8 mg liraglutide in 50 units of insulin degludec. After proving a superior efficacy over either insulin degludec or liraglutide alone with a lower incidence of hypoglycemia compared to an insulin therapy, IDegLira has now been approved in Europe for the treatment of type 2 diabetes in oral therapy failure or failure of therapy with basal insulin. The HbA1c reduction observed in the trials important for approval was approximately 1.9% with IDegLira showing an almost additive effect of the basal insulin and the GLP-1 RA [34]. Another fixed combination with lixisenatide and insulin glargine is in clinical development.

Extrapancreatic effects of GLP-1 receptor agonists

Gastric emptying and gastrointestinal transit time

Pharmacological doses of GLP-1 slow gastric emptying in a dose dependent manner, causing sensations of fullness up to transient nausea and vomiting. Because therapy with GLP-1 RA raises levels of a GLP-1 receptor ligand approximately eight- to ten-fold, treatment with these agents is often associated with transient nausea and vomiting. This side effect is more pronounced with short-acting GLP-1 RAs that show distinct peaks and troughs during therapy [4,35].

Weight loss

With the exception of albiglutide, all GLP-1 RAs caused significant weight loss in the magnitude of 1–3 kg in clinical studies lasting for 6 months [4,35]. Albiglutide, a large fusion protein of two GLP-1 molecules with albumin designed for once-weekly dosing appears to have less of an effect on body weight than other GLP-1 RAs, probably by not crossing the blood–brain barrier due to its molecular size and charge [4]. However, dulaglutide, which is also a large fusion protein, has been reported to result in similar

weight loss to exenatide and, therefore, the reduced effect of albiglutide may simply be due to reduced GLP-1 receptor stimulation [4,28,35].

In subjects without diabetes and obesity, clinical studies are ongoing or have been performed with GLP-1 RAs to observe the effects on body weight. For example, subjects treated with the maximal dose (3.0 mg) of liraglutide had a weight loss of approximately 10 kg after 2 years in a controlled study setting [4,35,36]. Liraglutide has now been approved in the US and the European Union for weight management and the treatment of obesity as an adjunct to diet and exercise.

Effects on the cardiovascular system

The GLP-1 RAs liraglutide and exenatide have demonstrated various beneficial aspects of cardiac function in animal models and cardiovascular risk factors in subjects with type 2 diabetes and long-term cardiovascular outcome trials are now ongoing. Along this line, significant reductions in biomarkers for cardiovascular risk (high sensitivity C-reactive protein [hsCRP], brain natriuretic protein [BNP], and plasminogen activator inhibitor-1 [PAI-1]) were observed in long-term studies with the GLP-1 RAs exenatide and liraglutide. Data from the 3.5-year extension of the exenatide Phase III program showed persistent and significant improvements in total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides [4,35].

In preclinical studies, GLP-1 RAs demonstrated cardioprotective effects such as reducing infarct size, improving cardiac output, and increasing survival after myocardial infarction (MI) in rodents; further mechanistic studies need to be carried out to fully characterize and understand the cardiovascular effects of GLP-1 [35]. A clinically meaningful reduction of the systolic blood pressure has been also been observed during treatment with GLP-1 RAs, ranging from 2–7 mmHg. For the diastolic blood pressure, the findings in a meta-analysis were not as consistent as for systolic blood pressure. The reduction in systolic blood pressure is independent from the weight loss that is also observed with GLP-1 RA therapy and is already present in early phases of treatment, when weight reduction has not occurred yet [4,35].

An increase in the heart rate of approximately 2–4 beats/minute was observed in clinical studies with GLP-1 RAs. This rise in pulse was persistent but not dose-dependent. The exact molecular mechanisms behind the GLP-1 RA-associated decrease in systolic blood pressure and increase in heart rate have not yet been fully elucidated. Mechanistic studies investigating acute effects as well as long-term clinical studies on the effects of GLP-1 RAs on hemodynamics and autonomic nervous system activity will be important to understand these changes. Furthermore, it is not clear yet if these effects might be predictors of cardiovascular outcomes [4,35].

Effects on cardiovascular outcomes

Analyses of the major adverse cardiovascular events (MACE) have been obtained from the clinical studies with GLP-1 RAs. With exenatide and liraglutide, the incidence ratio of MACE was not increased (and tended to be lower) compared with all comparator drugs pooled. For all the incretin-based therapies, large prospective cardiovascular safety and outcome trials are currently ongoing (Table 3.1) [37–41]. For lixisenatide, the results of the ELIXA study were presented at the 2015 Annual Scientific Meeting of the American Diabetes Association and showed non-inferiority of lixisenatide versus comparator therapy [42].

Pancreatic safety

Concerns regarding pancreatic safety with incretin-based therapies have been raised by a study which analyzed the pancreata from organ donors with or without type 2 diabetes [43]. An increase in endocrine pancreatic mass, exocrine duct cell proliferation, and dysplasia were described in the organs of people with a history of treatment with incretin-based therapies when compared to those who had not had incretin-based treatment [43]. The authors also suggested an increased risk for the evolution of neuroendocrine tumors [43]. However, following an investigation by the European Medicines Agency (EMA) and a hearing by the US Food and Drugs Administration (FDA), as well as several other publications, concerns have been raised about the methodology and sample size of the study. The general conclusions of the regulatory bodies EMA and FDA

Trial name/ clinicaltrial.gov ID	Drug	Target enrollment (n)	Trial timing (start; expected finish)
ELIXA/NCT01147250 [37]	lixisenatide	6,000	2010; ended 2014
EXSCEL/NCT01144338 [38]	exenatide	9,500	2010; ending 2017
LEADER/NCT01179048 [39]	liraglutide	9,340	2010; ending 2016
REWIND/NCT01394952 [40]	dulaglutide	9,622	2011; ending 2019
SUSTAIN6/NCT01720446 [41]	semaglutide	3,260	2013; ending 2016

Table 3.1 Cardiovascular safety trials with glucagon-like peptide-1 receptor agonists.

was that there should not be any substantial changes in clinical recommendations regarding the use of incretin-based therapies based on this study [44,45].

Individual analyses, pooled analyses, and meta-analyses of data from the clinical development programs of DPP-4 inhibitors and GLP-1 RAs, and analyses from claims databases have also reported no increased risk of pancreatitis with either class of agent when compared to comparator therapies [46,47]. Remaining ongoing long-term cardiovascular safety studies are being carried out on incretin-based therapies which will generate additional data on pancreatic safety in a large population of >60,000 patients [35]. These data will not be available until 2018 (Table 3.1).

Perspectives

The development of GLP-1 RAs has given patients with type 2 diabetes mellitus more therapeutic options and has opened up the possibility of improving glycemic control without the concomitant risk of hypoglycemia. These drugs also offer the opportunity to achieve both improved glycemic control and a reduction in body weight. The percentage of patients reaching their glycemic targets during therapy with GLP-1 RAs has been greater than that achieved with most established therapies for type 2 diabetes [4,35].

GLP-1 RA therapy may have beneficial effects beyond the glycemic effects by direct action on the endocrine pancreas due to the widespread expression of GLP-1 receptors. These may include effects on cardiovascular health, lipid metabolism, neurological disorders, systolic blood pressure, and body weight. These beneficial effects need to be counterweighed against possible side effects (eg, gastrointestinal side effects, increased pulse rate). Data from the ongoing long-term safety studies are needed

to confirm if the beneficial effects seen in preclinical studies and shorter clinical trials will also improve long-term outcomes.

GLP-1 RAs may also have potential to be used in treating obesity. Liraglutide has been recently approved for this indication in the US and European Union and substantial further research in people without diabetes is underway to test this hypothesis. Studies are also ongoing to elucidate the effects of GLP-1 RAs in the treatment of type 1 diabetes in conjunction with insulin therapy. Here, the effects of the GLP-1 RA on gastric emptying and glucagon secretion may have beneficial effects on glycemic control [4,35].

References

1 Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists. *Lancet*. 2006;368:1696-1705.

2 Gallwitz B. Glucagon-like peptide-1 analogues for type 2 diabetes mellitus: current and emerging agents. *Drugs*. 2011;71:1675-1688.

3 Madsbad S, Kielgast U, Asmar M, Deacon CF, Torekov SS, Holst JJ. An overview of once-weekly glucagon-like peptide-1 receptor agonists--available efficacy and safety data and perspectives for the future. *Diabetes Obes Metab*. 2011;13:394-407.

4 Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2012;8:728-742.

5 Raufman JP, Singh L, Singh G, Eng J. Truncated glucagon-like peptide-1 interacts with exendin receptors on dispersed acini from guinea pig pancreas. Identification of a mammalian analogue of the reptilian peptide exendin-4. *J Biol Chem*. 1992;267:21432-21437.

6 Gallwitz B, Guzman J, Dotta F, et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. *Lancet*. 2012;379:2270-2278.

7 Nauck MA, Incretin-based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications. *Am J Med*. 2011;124:S3-S18.

8 Kim D, MacConell L, Zhuang D, et al. Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. *Diabetes Care*. 2007;30:1487-1493.

9 Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet*. 2008;372:1240-1250.

10 Buse JB, Drucker DJ, Taylor KL, et al. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. *Diabetes Care*. 2010;33:1255-1261.

11 Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin*. 2008;24:275-286.

12 Fineman MS, Mace KF, Diamant M, et al. Clinical relevance of anti-exenatide antibodies: safety, efficacy and cross-reactivity with long-term treatment. *Diabetes Obes Metab*. 2012;14:546-554.

13 Agerso H, Jensen LB, Elbrond B, Rolan P, Zdravkovic M. The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. *Diabetologia*. 200245:195-202.

14 Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet*. 2009;374:39-47.

15 Pratley RE, Nauck M, Bailey T, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet*. 2010;375:1447-1456

16 Ratner RE, Rosenstock J, Boka G; DRI6012 Study Investigators. Dose-dependent effects of the once-daily GLP-1 receptor agonist lixisenatide in patients with Type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled trial. *Diabet Med*. 2010;27:1024-1032.

17 Forst T, Pfützner A. Pharmacological profile, efficacy and safety of lixisenatide in type 2 diabetes mellitus. *Expert Opin Pharmacother*. 2013;14:2281-2296

18 Petersen AB, Knop FK, Christensen M. Lixisenatide for the treatment of type 2 diabetes. *Drugs Today (Barc)*. 2013;49:537-553.

19 Rosenstock J, Raccah D, Korányi L, et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). *Diabetes Care*. 2013;36:2945-2951.

20 Kapitza C, Forst T, Coester HV, et al. Pharmacodynamic characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin. *Diabetes Obes Metab*. 2013;15:642-649.

21 Trujillo JM, Nuffer W. Albiglutide: a new GLP-1 receptor agonist for the treatment of type 2 diabetes. *Ann Pharmacother*. 2014;48:1494-1501.

22 Home PD, Shamanna P, Stewart M, et al. Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5. *Diabetes Obes Metab*. 2015;17:179-187.

23 Weissman PN, Carr MC, Ye J, et al. HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. *Diabetologia*. 2014;57:2475-2484.

24 Reusch J, Stewart MW, Perkins CM, et al. Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin. *Diabetes Obes Metab*. 2014;16:1257-1264.

25 Ahrén B, Johnson SL, Stewart M, et al. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. *Diabetes Care*. 2014;37:2141-2148.

26 Rosenstock J, Fonseca VA, Gross JL, et al. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. *Diabetes Care*. 2014;37:2317-2325.

27 Pratley RE, Nauck MA, Barnett AH, et al. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. *Lancet Diabetes Endocrinol*. 2014;2:289-297.

28 Amblee A. Dulaglutide for the treatment of type 2 diabetes. *Drugs Today (Barc)*. 2014;50:277-289.

29 Barrington P, Chien JY, Showalter HD, et al. A 5-week study of the pharmacokinetics and pharmacodynamics of LY2189265, a novel, long-acting glucagon-like peptide-1 analogue, in patients with type 2 diabetes. *Diabetes Obes Metab*. 2011;13:426-433.

30 Giorgino F, Benroubi M, Sun JH, et al. Efficacy and safety of once weekly dulaglutide vs insulin glargine in combination with metformin and glimepiride in type 2 diabetes patients (AWARD-2). *Diabetologia* 2014;57 (suppl 1):OP38.

31 O'Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, Phase 3, non-inferiority trial. *Lancet*. 2014;384(9951):1349-1357.

32 Thompson AM, Trujillo JM. Dulaglutide: the newest GLP-1 receptor agonist for the management of type 2 diabetes. *Ann Pharmacother*. 2015;49:351-359.

33 Gotfredsen CF, Mølck AM, Thorup I, et al. The human GLP-1 analogs liraglutide and semaglutide: absence of histopathological effects on the pancreas in nonhuman primates. *Diabetes*. 2014;63:2486-2497.

34 Gough SC, Bode B, Woo V, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. *Lancet Diabetes Endocrinol*. 2014;8587:70174-70173.

35 Seufert J, Gallwitz B. The extra-pancreatic effects of GLP-1 receptor agonists: a focus on the cardiovascular, gastrointestinal, and central nervous systems. *Diabetes Obes Metab*. 2014;16:673-688.

36 Astrup A, Carraro R, Finer N, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond)*. 2012;36:843-854.

37 Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide) (ELIXA). http://clinicaltrials.gov/ct2/show/NCT01147250. Accessed October 5, 2015.

38 Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL): A Trial To Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus. http://clinicaltrials.gov/ct2/show/NCT01144338. Accessed October 5, 2015.

39 Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results - A Long Term Evaluation (LEADER®). http://clinicaltrials.gov/ct2/show/NCT01179048.

40 Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND). http://clinicaltrials.gov/ct2/show/NCT01394952. Accessed October 5, 2015.

41 Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL): A Trial To Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus. http://clinicaltrials.gov/ct2/show/NCT01720446. Accessed October 5, 2015.

42 Pfeffer MA. The evaluation of lixisenatide in acute coronary syndrome - the results of ELIXA. Results -- cardiovascular outcomes. Webcast presentation at American Diabetes Association 75th Annual Scientific Sessions, June 5-9th, Boston, Massachusetts. http://professional.diabetes.org/Presentations_Details.aspx?session=4740. Accessed October 5, 2015.

43 Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes*. 2013;62:2595-2604.

44 European Medicines Agengy (EMA). Investigation into GLP-1-based diabetes therapies concluded. www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/07/news_detail_001856.jsp&mid=WC0b01ac058004d5c1. Accessed October 5, 2015.

45 Food and Drug Administration (FDA). FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes. www.fda.gov/Drugs/DrugSafety/ucm343187.htm. Accessed October 5, 2015.

46 Li L, Shen J, Bala MM, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. *BMJ*. 2014;348:g2366.

47 Meier JJ, Nauck MA. Risk of pancreatitis in patients treated with incretin-based therapies. *Diabetologia*. 2014;57:1320-1324.

Chapter 4

Dipeptidyl peptidase-4 inhibitors

Carolyn F Deacon

Introduction

Dipeptidyl peptidase (DPP)-4 inhibitors inhibit the activity of the enzyme responsible for the initial rapid degradation of the incretin hormones, thereby enhancing their antihyperglycemic effects. The first DPP-4 inhibitor to be approved for treatment of type 2 diabetes was sitagliptin in 2006 and there are now eight available: alogliptin, linagliptin, saxagliptin, and vildagliptin, all with relatively broad global availability, and anagliptin, gemigliptin, and teneligliptin with currently more restricted geographical availability. Several other inhibitors are in various stages of clinical development. This review will focus on the five most commonly used inhibitors.

Pharmacokinetics and pharmacodynamics

As a class, DPP-4 inhibitors comprise a group of structurally diverse, orally available small molecules [1]. They all bind reversibly to the DPP-4 enzyme, but whereas alogliptin, linagliptin, and sitagliptin form non-covalent interactions with sites in the catalytic pocket, saxagliptin and vildagliptin bind covalently. Alogliptin, linagliptin and sitagliptin have intrinsically long half-lives; they do not undergo appreciable metabolism and are eliminated slowly, resulting in sustained DPP-4 inhibition and allowing for a once daily dosing regimen (Table 4.1). In contrast, saxagliptin and vildagliptin are metabolized extensively.

Hepatic metabolism of saxagliptin generates an active metabolite which is half as potent as the parent compound. Following administration,

S. Gough (ed.), *Handbook of Incretin-based Therapies in Type 2 Diabetes*, DOI 10.1007/978-3-319-08982-9_4

	Metabolism	Elimination route	Half-life (hours)	DPP-4 inhibition (24-hours post-dose)	Dose*
alogliptin	Limited	Predominantly renal	~ 21	~ 75%	25 mg qd
linagliptin	Limited	Predominantly biliary (< 6% renal)	~ 12 (effective) > 100 (terminal)	> 80%	5 mg qd
saxagliptin	Active metabolite (hepatic via CYP3A4/5)	Metabolism (parent) Renal (parent + metabolite)	~ 2.5 (parent) ~ 3 (metabolite)	~ 70%	5 mg qd
sitagliptin	Limited	Predominantly renal	~ 12.5	> 80%	100 mg qd
vildagliptin	Inactive metabolite (CYP-independent hydrolysis)	Metabolism (parent) Renal (parent + metabolite)	~ 2	< 40% (~80% 12h post-dose)	50 mg bid

Table 4.1 Characteristics of dipeptidyl peptidase-4 (DPP-4) inhibitors. Data taken from [1] and the prescribing information of the individual inhibitors. *Dose may vary in some countries. bid, twice daily; qd, once daily.

approximately one-quarter of the inhibitor circulates as the intact saxagliptin molecule and one-half as the metabolite. Vildagliptin undergoes hydrolysis, forming a pharmacologically inactive metabolite; around one-fifth circulates as the active inhibitor. Consequently, both saxagliptin and vildagliptin have short half-lives (Table 4.1). Nevertheless, DPP-4 activity is inhibited for longer than would be predicted because the inhibitors remain bound to the enzyme until slow hydrolysis breaks the covalent bonds, meaning that saxagliptin can be used once daily and vildagliptin twice daily. Accordingly, despite the differences in half-life, direct comparison reveals that the extent of DPP-4 inhibition obtained with sitagliptin and vildagliptin is comparable (and greater than that achieved with saxagliptin) when the inhibitors are used at their therapeutic doses (once daily for saxagliptin and sitagliptin, twice daily for vildagliptin) [2].

The kidney plays an important role in the elimination of all of the inhibitors, with the exception of linagliptin. Thus, both alogliptin and sitagliptin are predominantly renally eliminated (as the parent

molecules) via mechanisms involving both active secretion as well as glomerular filtration, whereas saxagliptin and vildagliptin are subjected to metabolism, as described above, with subsequent renal clearance. In contrast, linagliptin is mostly protein-bound at its therapeutic dose, which minimizes its renal clearance (to <6%); the main route of elimination is biliary excretion [1].

Efficacy

Although there are some differences in the indications for the individual agents, as a class, DPP-4 inhibitors have been approved for use as monotherapy (for patients in whom metformin is not indicated or not tolerated) and as add-on combination therapy (dual and triple therapy with metformin, sulphonylureas, thiazolidinediones, insulin) if treatment goals are not met with metformin alone. Their efficacy, as monotherapy and in combination with other agents, has now been demonstrated in numerous clinical trials, where they typically result in reductions in HbA1c of 0.6–1.0% (dependent on baseline levels, with reductions of up to ~2% being seen in subjects with elevated HbA1c concentrations). In head-to-head comparisons, the DPP-4 inhibitors generally result in smaller HbA1c reductions in monotherapy compared to metformin but they have consistently been demonstrated to be equivalent to sulphonylureas and thiazolidinediones, particularly when used as add-on therapy to metformin (Figure 4.1) [3]. However, despite their similar glycemic efficacy, the DPP-4 inhibitors are not associated with hypoglycemia and are generally weight neutral, in contrast to the increased risk of hypoglycemia, which is characteristically seen with the sulphonylureas, and the weight gain associated with both sulphonylureas and thiazolidinediones [3].

Dipeptidyl peptidase-4 inhibitors monotherapy

While metformin will still be the preferred option for most patients, there is an increasing place for DPP-4 inhibitors to be used in monotherapy when metformin cannot be used. While their efficacy is similar to that of other agents which might be used in this situation, their tolerability/side effect profile is generally superior. Thus, in cases where monotherapy with metformin is not a suitable option, the glucose-dependent mechanism of

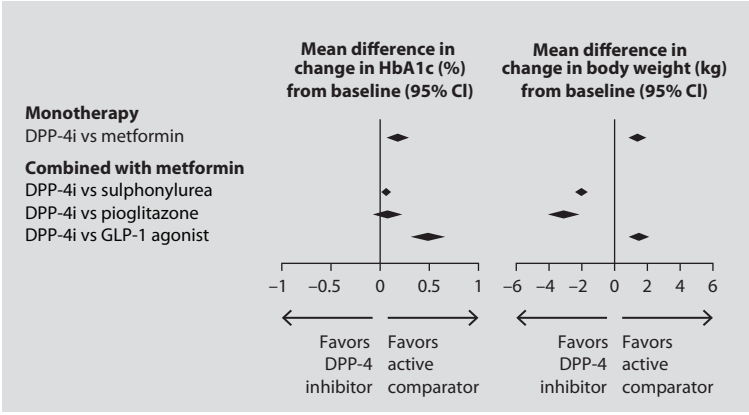

Figure 4.1 Meta-analysis showing glycated hemoglobin (HbA1c)-lowering efficacy and body weight effects of dipeptidyl peptidase inhibitors (DPP-4i) as monotherapy compared with metformin or as add-on therapy to metformin when compared with other commonly used antihyperglycemia agents combined with metformin. Based on data published from Phase III clinical trials of ≥16 weeks duration. Data are shown as mean difference between DPP-4 inhibitors and comparators in the change from baseline (± 95% confidence intervals [CI]). GLP-1, glucagon-like peptide. Figure modified with permission from Karagiannis et al [3] ©BMJ.

action associated with DPP-4 inhibitors may favor their use, particularly in patients where hypoglycemia should be avoided (eg, drivers of goods vehicles, operators of heavy machinery), in the elderly, and in those at higher risk from hypoglycemia due to comorbidities (eg, kidney disease).

Combination therapy

Combination with metformin

DPP-4 inhibitors are positioned as second-line agents in many therapeutic guidelines, including the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement [4] and the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) diabetes algorithms [5,6]. They are commonly used in addition to ongoing metformin therapy if therapeutic targets are not attained. Fixed-dose combinations with metformin are now available with all of the individual inhibitors, giving the option of a twice-daily dosing regimen (when combined with immediate-release metformin), or once daily use (when combined with the extended-release metformin formulation). The combination of

metformin with a DPP-4 inhibitor has its merits because it effectively targets the underlying pathology of type 2 diabetes, with metformin improving insulin resistance and directly reducing hepatic glucose output, while the DPP-4 inhibitors address islet dysfunction (and indirectly, endogenous glucose production) via insulinotropic and glucagonostatic effects mediated through GLP-1.

However, they do this without increasing the risk of hypoglycemia or weight gain. Indeed, the AACE consensus statement positions DPP-4 inhibitors ahead of the sulphonylureas because of their lower hypoglycemia risk and the absence of weight gain [5,6]. The metformin/DPP-4 inhibitor combination gives rise to greater HbA1c lowering than when either agent is used alone and, intriguingly, is associated with a reduced incidence of gastrointestinal side effects than when metformin is used as monotherapy [7]; the mechanism behind this effect has yet to be elucidated. Because of its greater efficacy compared to metformin monotherapy, initial combination therapy including a DPP-4 inhibitor is also recommended in patients with elevated HbA1c levels at diagnosis in some guidelines (eg, AACE/ACE) [5,6]. Indeed, when baseline HbA1c levels are >10%, reductions in HbA1c of >3% can be achieved with initial combination therapy, compared to ~2.5% when therapy is initiated with metformin alone [8,9].

Combination with sulphonylurea

The use of DPP-4 inhibitors together with sulphonylureas has also been approved as dual therapy or as part of triple therapy in combination with metformin. While the combination gives additional glycemic efficacy, the risk of hypoglycemia is increased in comparison to combinations not including a sulphonylurea. Thus, although DPP-4 inhibitors have a glucose-dependent mechanism of action (ie, insulin secretion is stimulated and glucagon secretion suppressed only when glucose levels rise above fasting levels), which minimizes the risk of hypoglycemia; this glucose-dependency is uncoupled in the presence of the sulphonylurea [10]. Accordingly, a reduction in the sulphonylurea dose is recommended when used concomitantly with a DPP-4 inhibitor.

Combination with insulin

Although perhaps not initially considered an obvious combination, the use of DPP-4 inhibitors together with insulin has been shown to be of benefit and is increasingly being used. A number of studies have examined the effect of adding a DPP-4 inhibitor in patients inadequately treated with insulin, showing that additional glycemic control can be obtained. While some studies reported a minor increase in hypoglycemia following the addition of the DPP-4 inhibitor [11], this was attributed to the study design (change in the insulin dose was not permitted unless hypoglycemia occurred); in studies where the insulin dose could be titrated, no such increase in hypoglycemia was noted [12]. This combination is associated with an insulin-sparing effect, and improvements in glycemic control can be obtained with smaller increments in insulin dosage following the addition of a DPP-4 inhibitor to insulin in placebo-controlled studies [13].

In studies designed to more closely mimic real world settings, the effect of intensification of insulin therapy has been compared against adding a DPP-4 inhibitor to ongoing therapy. These studies showed that not only could glycemic control be improved despite the lower insulin dose when a DPP-4 inhibitor was added, but the incidence of hypoglycemia was also reduced [14]. Beneficial effects are also seen when insulin is added to an ongoing regimen, which includes a DPP-4 inhibitor. Thus, in subjects inadequately treated with metformin and a DPP-4 inhibitor, the addition of insulin glargine resulted in additional HbA1c reductions without unduly increasing the risk of hypoglycemia or weight gain [15].

Use in specific patient populations

Renal impairment

All DPP-4 inhibitors can be used in patients with reduced renal function (Table 4.2), although once creatinine clearance declines below 50 mL/min, dose adjustment is required for those inhibitors with a renal route of elimination (alogliptin, saxagliptin, sitagliptin, vildagliptin). This is not for safety reasons, but rather to compensate for the increase in exposure which occurs once renal function declines [1]. Accordingly, for alogliptin and sitagliptin (which depend predominantly on the kidneys for their elimination), doses are reduced by one-half (moderate renal

impairment) and one-quarter (severe renal impairment, including end-stage renal disease and dialysis), whereas for saxagliptin and vildagliptin (which undergo metabolism as well as renal elimination), a single dose reduction is sufficient (Table 4.2). Renal function should be monitored to allow appropriate dose choice, although this is not required for linagliptin because of its primarily non-renal route of elimination. However, given the wide therapeutic window, it is doubtful that any drug accumulation would lead to unfavorable outcomes if the normal therapeutic doses are inadvertently used in subjects with impaired renal function [16].

The degree of improvement in glycemic control attained with DPP-4 inhibitors in renally impaired subjects, including those on dialysis, is similar to that observed in subjects without kidney disease and, as is also seen in individuals with normal renal function, DPP-4 inhibitors lower HbA1c levels to a comparable extent as other anti-hyperglycemic agents in patients with reduced kidney function [16]. In line with the glucose-dependency of their action, the incidence or severity of hypoglycemia is not increased, an important consideration in this patient group where renal impairment itself is a risk factor for hypoglycemia [16]. This, coupled with their good tolerability and absence of any increase in the incidence or severity of other adverse events makes them an attractive therapeutic option in patients with diabetes and kidney disease, particularly since many other agents may have restricted use or be contraindicated in this population [17].

Hepatic impairment

Generally speaking, reduced liver function is not a contraindication for the use of DPP-4 inhibitors, although experience in patients with severe hepatic impairment is more limited (Table 4.2). Vildagliptin has been associated with mild increases in liver transaminases, although not with any increase in actual hepatic adverse events [18]. Monitoring of liver function is, therefore, recommended prior to initiation of therapy of vildagliptin and its use is not recommended in patients with any degree of hepatic impairment, including pre-treatment elevated liver enzyme levels.

Elderly and vulnerable patients

DPP-4 inhibitors appear particularly well-suited for use in vulnerable patient groups because of their ease of use, low risk of hypoglycemia, and absence of side effects or weight gain. Management of elderly patients with diabetes can be challenging because this group is often characterized by the presence of long-standing diabetes, a high prevalence of comorbidities including an age-related decline in renal function, the use of multiple concomitant drugs, and progressive cognitive impairment. Moreover, given that many of these patients are also frail, the consequences of hypoglycemia (eg, falls resulting in hip fractures) can be more severe and occur with greater frequency.

Data from post-hoc subgroup analyses of Phase III clinical trials, as well as from specific prospective studies in elderly subjects, confirm not only the efficacy of DPP-4 inhibitors in this patient group, but importantly also show them to be well tolerated and without increased risk of hypoglycemia [19]. Along similar lines, the overall good safety profile of the DPP-4 inhibitors makes them a good option for treatment of individuals with psychiatric disorders where a risk of overdose may exist [20].

Safety

To date, the DPP-4 inhibitor class appears to have a good safety profile [21] and early suggestions that they may compromise immune function and be associated with increased risk of infections have not been realized [3]. Numerous pooled safety analyses, meta-analyses, and data-base analyses have generally indicated that the DPP-4 inhibitors are associated with good tolerability and have an adverse event profile, that is similar to that of placebo [22]. However, occasional findings and isolated post-marketing observations have led to some debate over potential safety issues [22].

Acute pancreatitis

Post-marketing reports of acute pancreatitis in some patients taking incretin-based therapies led to warnings about the risk of pancreatitis being included in the prescribing information of all DPP-4 inhibitors (and GLP-1 receptor agonists) [22]; whether or not there is a causal relationship has still not been fully resolved. Animal studies have provided conflicting

Drug	Renal function monitoring	Renal impairment			Liver function monitoring	Hepatic impairment		Use with other drugs†
		Mild (CrCl ≥50 ml/min)	Moderate (CrCl ≥30-<50ml/min)	Severe/ESRD (CrCl <30ml/min)		Mild/ Moderate	Severe	
alogliptin	Yes	Yes	Yes, with dose adjustment (12.5 mg qd)	Yes, with dose adjustment (6.25 mg qd)	No	Yes	NR	–
linagliptin	No	Yes	Yes	Yes	No	Yes	Yes	Efficacy may be reduced if used with CYP3A4 inducer (eg, rifampin)
saxagliptin	Yes	Yes	Yes, with dose adjustment (2.5 mg qd)	Yes, with dose adjustment (2.5 mg qd)*	No	Yes	NR	Dose reduction (2.5mg qd) when used with strong CYP3A4/5 inhibitors (eg, ketoconazole; ritonavir).
sitagliptin	Yes	Yes	Yes, with dose adjustment (50 mg qd)	Yes, with dose adjustment (25 mg qd)	No	Yes	Not studied	–
vildagliptin	Yes	Yes	Yes, with dose adjustment (50 mg qd)	Yes, with dose adjustment (50mg qd)**	Yes	No*	No*	Dose reduction (50mg qd) when used with sulphonylurea

Table 4.2 Prescribing characteristics of commonly used dipeptidyl peptidase-4 (DPP-4) inhibitors. Data taken from prescribing information of the individual inhibitors; precise indications may vary by country). *Including those with transaminase levels ≥3 times upper limit of normal.†Dose reduction of sulphonylurea or insulin may be recommended when used together with a DPP-4 inhibitor. CrCl, creatinine clearance; CYP3A4/5, cytochrome P450, family 3, subfamily A, polypeptide 4/5; ESRD, end-stage renal disease; NR, not recommended. *Not recommended for patients requiring hemodialysis. **Use with caution for patients undergoing hemodialysis.

results: a few have described deleterious histological changes in the exocrine pancreas whereas others have been neutral, or even suggestive of protective actions in models of experimentally-induced pancreatitis [22]. These studies have mostly been carried out in rodents, however, and as such, are not necessarily predictive of the situation in humans. In the clinical trials [22], the incidence of acute pancreatitis has been very low, and pooled safety analyses have not given rise to any signal. Similarly, the majority of retrospective meta-analyses and observational studies have also concluded that there is no increased risk, although there have been one or two isolated reports contradicting this viewpoint [22].

Concern over this potential safety issue led the regulatory authorities in both the US and EU to undertake independent reviews of all the data, with the conclusion being that currently available data do not support a causal association between incretin-based therapies and pancreatitis [23]. A similar viewpoint has been taken by the major diabetes societies (eg, ADA, EASD, International Diabetes Federation), who have issued a joint statement indicating that there is presently no need to modify current treatment recommendations concerning the use of incretin-based therapies [24]. Encouragingly, the rates of acute pancreatitis were low in the three recently completed large cardiovascular safety studies with DPP-4 inhibitors [25–27]. There were, however, small numerical imbalances in the number of events and although these differences were not significant, it cannot be fully dismissed that a minor increase in risk may exisit. A recent pooled analysis (including the first two of these studies, as well as Phase II clinical trials) confirmed the low event rate (1.3 vs 1.2 events per 1,000 patient-years of exposure for DPP-4 inhibitors and comparators, respectively) and the apparent lack of increased risk (Figure 4.2) [28].

Cancer

While toxicology studies, clinical trials, and pooled safety analyses have not given cause for concern (Figure 4.3) [21,22], the question of whether DPP-4 inhibitors may be associated with chronic pancreatitis and increased risk of pancreatic cancer has been raised. This issue has also been thoroughly investigated by the FDA and EMA, as well as by

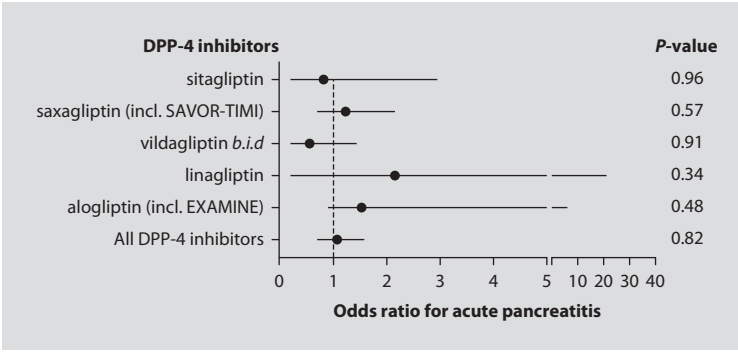

Figure 4.2 Pooled analysis showing risk of acute pancreatitis for DPP-4 inhibitors compared against placebo and active comparators. Based upon data of pancreatitis events from Phase III clinical trials on linagliptin, saxagliptin, sitagliptin, together with data extracted from a published pooled safety analysis (vildagliptin) and two cardiovascular outcome studies (SAVOR-TIMI, EXAMINE). Data are shown as odds ratios (OR) ± 95% confidence intervals. bid, twice a day. Figure modified with permission from Meier and Nauck [28] ©Springer.

the major diabetes societies; no evidence was found to suggest a causal link [23,24]. Additionally, there were no signals for any increase in cancer risk, including pancreatic cancer in any of the three completed cardiovascular safety trials [25–27].

Cardiovascular safety

Pooled safety analyses, as well as retrospective meta-analyses of clinical trials and healthcare providers' databases, have all consistently indicated that DPP-4 inhibitors are not associated with any increase in cardiovascular adverse events, and have even pointed towards a risk reduction [29]. However, these studies are generally of relatively short duration and do not typically include subjects at elevated cardiovascular risk or those with established cardiovascular disease. Large prospective outcome studies of longer duration in high risk populations (EXAMINE: alogliptin [30]; CARMELINA: linagliptin [31]; SAVOR-TIMI: saxagliptin [32]; TECOS: sitagliptin [33], all placebo-controlled; and CAROLINA: linagliptin [34] vs active comparator [glimepiride]) have, therefore, been undertaken to evaluate cardiovascular safety. Vildagliptin is not marketed in the US; hence; there is no large cardiovascular outcome trial with this compound.

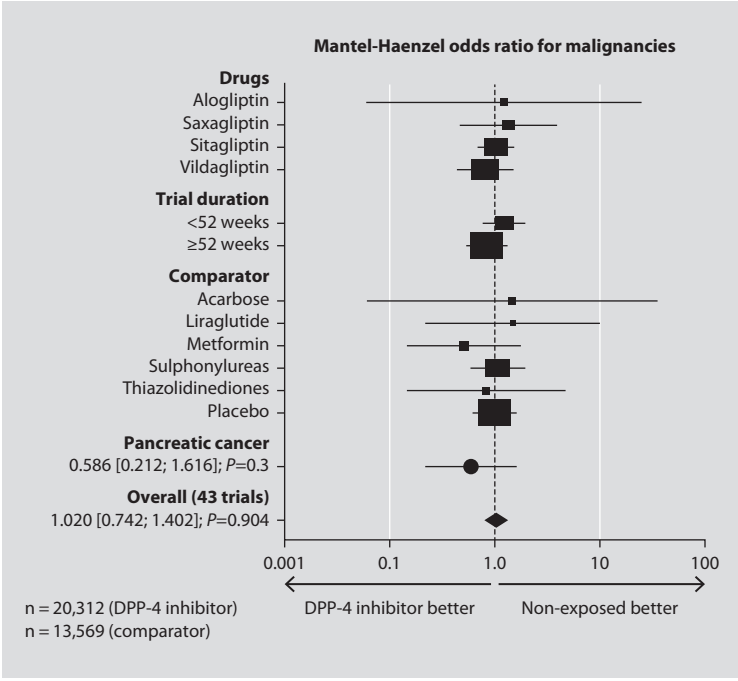

Figure 4.3 Meta-analysis showing risk of malignancies for DPP-4 inhibitors compared against placebo and active comparators. Based on data published from Phase III clinical trials of ≥24 weeks duration. Data are shown as odds ratios ± 95% confidence intervals. Figure adapted with permission from Monami et al [21] ©Informa.

Reassuringly, the first three of these outcome trials to report their findings (EXAMINE [25], SAVOR-TIMI [35], and TECOS [27]) have confirmed that neither alogliptin (5,400 patients with recent acute coronary syndrome; mean follow-up 1.5 years), saxagliptin (16,500 patients with pre-existing cardiovascular disease or multiple risk factors; mean follow-up period of 2.1 years), nor sitagliptin (14,600 patients with established cardiovascular disease; mean follow-up of 3.0 years) was associated with any increase in mortality compared to placebo (hazard ratios for the primary composite cardiovascular outcome [cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and in EXAMINE, hospitalization for unstable angina] of 0.96, 1.00 and 0.98, respectively). However, neither was there any reduction in cardiovascular risk.

Unexpectedly, a small increase in the rate of hospitalization for heart failure was noted in SAVOR-TIMI (hazard ratio 1.27; 95% CI, 1.07–1.51), with further analysis suggesting that subjects at greatest risk were those with previous heart failure, an estimated glomerular filtration rate ≤60 mL/min, or elevated baseline levels of N-terminal pro B-type natriuretic peptide [35,36]. Notably, however, the increased risk of hospitalization for heart failure in SAVOR-TIMI was not associated with any increase in adverse outcomes and its clinical significance is unknown [35,36]. In post hoc analyses of the results of EXAMINE, despite a small numerical imbalance, the rate of hospitalization for heart failure did not differ significantly between alogliptin and placebo treatment (hazard ratio 1.19; 95% CI, 0.90–1.58), and there was no indication that alogliptin led to any increase in new hospital admissions for heart failure or worsened outcomes for patients with a previous history of heart failure [37]. There was no signal for any increase in the risk of hospitalization for heart failure in TECOS, with the incidence (3.1%) being identical in both arms of the trial (hazard ratio 1.00; 95% CI, 0.83–1.20) [27]. At present, there is no obvious mechanistic explanation for the increased heart failure hospitalization seen in SAVOR-TIMI and it remains uncertain whether there is any causal relationship to DPP-4 inhibition, per se.

Conclusions

DPP-4 inhibitors have been on the market for nearly a decade and have now become an established therapy option for diabetes. Clinical experience has shown them to be effective, both when used in monotherapy or to provide additional glycemic control when used in combination. They can be used at all stages of disease progression, from diagnosis through to patients with long-standing diabetes, and are effective in all patient groups, including those with renal or hepatic impairment. DPP-4 inhibitors probably belong to the class of antihyperglycemic agents which currently has the best studied safety profile, showing them to be well tolerated: they generally do not provoke hypoglycemia, they are weight neutral and, so far, seem to be associated with a broadly benign adverse effect profile. Potential safety concerns over the possibility of a

small increased risk of acute pancreatitis still remain to be resolved; at present, no causal relationships have been established.

Ongoing pharmacovigilance, together with accumulating data from the large outcome trials, will reveal more about the long-term safety of the DPP-4 inhibitors. However, even if any of the potential safety concerns are proven, it should be borne in mind that the absolute risks involved are small, so the clinical relevance of any potential small increase is likely to be limited and should be evaluated for the individual patient based on a risk-benefit judgment. DPP-4 inhibitors, therefore, provide another choice for individualized therapy to help the patient achieve and maintain their glycemic targets which, in the longer term, may help to reduce diabetic complications and improve quality of life.

References

1 Deacon CF. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes Metab.* 2011;13:7-18.

2 Tatosian DA, Guo Y, Schaeffer AK, et al. Dipeptidyl peptidase-4 inhibition in patients with type 2 diabetes treated with saxagliptin, sitagliptin, or vildagliptin. *Diabetes Ther.* 2013;4:431-442.

3 Karagiannis T, Paschos P, Paletas K, et al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. *BMJ.* 2012;344:e1369.

4 Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia.* 2012;55:1577-1596.

5 Rodbard HW, Jellinger PS, Davidson JA, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract.* 2009;15:540-559.

6 Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement – executive summary. *Endocr Pract.* 2013;19:536-557.

7 Reasner C, Olansky L, Seck TL, et al. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. *Diabetes Obes Metab.* 2011;13:644-652.

8 Williams-Herman D, Johnson J, Teng R, et al. Efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes: a 54-week study. *Curr Med Res Opin.* 2009;25:569-583.

9 Bosi E, Dotta F, Jia Y, Goodman M. Vildagliptin plus metformin combination therapy provides superior glycemic control to individual monotherapy in treatment-naive patients with type 2 diabetes mellitus. *Diabetes Obes Metab.* 2009;11:506-515.

10 de Heer J, Holst JJ. Sulfonylurea compounds uncouple the glucose dependence of the insulinotropic effect of glucagon-like peptide 1. *Diabetes.* 2007;56:438-443.

11 Vilsbøll T, Rosenstock J, Yki-Järvinen H, et al. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. *Diabetes Obes Metab.* 2010;12:167-177.

12 Kothny W, Foley J, Kozlovski P, Shao Q, Gallwitz B, Lukashevich V. Improved glycemic control with vildagliptin added to insulin, with or without metformin, in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2013;15:252-257.

13 Barnett AH, Charbonnel B, Li J, Donovan M, Fleming D, Iqbal N. Saxagliptin add-on therapy to insulin with or without metformin for type 2 diabetes mellitus: 52-week safety and efficacy. *Clin Drug Investig.* 2013;33:707-717.

14 Hong ES, Khang AR, Yoon JW, et al. Comparison between sitagliptin as add-on therapy to insulin and insulin dose-increase therapy in uncontrolled Korean type 2 diabetes: CSI study. *Diabetes Obes Metab.* 2012;14:795-802.

15 Seufert J, Pegelow K, Bramlage P. Efficacy and safety of insulin glargine added to a fixed-dose combination of metformin and a dipeptidyl peptidase-4 inhibitor: results of the GOLD observational study. *Vasc Health Risk Manag.* 2013;9:711-777.

16 Davis TM. Dipeptidyl peptidase-4 inhibitors: pharmacokinetics, efficacy, tolerability and safety in renal impairment. *Diabetes Obes Metab.* 2014;16:891-899.

17 Scheen AJ. Pharmacokinetic considerations for the treatment of diabetes in patients with chronic kidney disease. *Expert Opin Drug Metab Toxicol.* 2013;9:529-550.

18 Ligueros-Saylan M, Foley JE, Schweizer A, et al. An assessment of adverse effects of vildagliptin versus comparators on the liver, the pancreas, the immune system, the skin and in patients with impaired renal function from a large pooled database of Phase II and III clinical trials. *Diabetes Obes Metab.* 2010;12:495-509.

19 Avogaro A, Dardano A, de Kreutzenberg SV, Del Prato S. Dipeptidyl peptidase-4 inhibitors can minimize the hypoglycemic burden and enhance safety in elderly people with diabetes. *Diabetes Obes Meta*b. 2015;17:107-115.

20 Furukawa S, Kumagi T, Miyake T, et al. Suicide attempt by an overdose of sitagliptin, an oral hypoglycemic agent: a case report and a review of the literature. *Endocr J.* 2012;59:329-333.

21 Monami M, Dicembrini I, Martelli D, Mannucci E. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. *Curr Med Res Opin.* 2011;suppl 3:57-64.

22 Deacon CF, Holst JJ. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes: comparison, efficacy and safety. *Expert Opin Pharmacother* 2013;14:2047-2058

23 Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs--FDA and EMA assessment. *N Engl J Med.* 2014;370:794-797.

24 ADA/EASD/IDF recommendations for clinicians and people with diabetes concerning the use of incretin therapy and pancreatic disease. EASD website. http://easd.org/index.php?option=com_content&view=article&id=172. Accessed October 5, 2015.

25 White W, Cannon C, Heller S, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med.* 2013;369:1327-1335.

26 Raz I, Bhatt DL, Hirshberg B, et al. Incidence of pancreatitis and pancreatic cancer in a randomized controlled multicenter trial (SAVOR-TIMI 53) of the dipeptidyl peptidase-4 Inhibitor saxagliptin. *Diabetes Care.* 2014;37:2435-2441.

27 Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373:586.

28 Meier JJ, Nauck MA. Risk of pancreatitis in patients treated with incretin-based therapies. *Diabetologia*. 2014;57:1320-1324.

29 Karagiannis T, Boura P, Tsapas A. Safety of dipeptidyl peptidase 4 inhibitors: a perspective review. *Ther Adv Drug Saf*. 2014;5:138-146.

30 White WB, Bakris GL, Bergenstal RM, et al. EXamination of cArdiovascular outcoMes with alogliptin versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. *Am Heart J*. 2011;162:620-626.

31 CARMELINA: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus. https://clinicaltrials.gov/ct2/show/NCT01897532. Accessed October 5, 2015.

32 Scirica BM1, Bhatt DL, Braunwald E, et al. The design and rationale of the saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus-thrombolysis in myocardial infarction (SAVOR-TIMI) 53 study. *Am Heart J*. 2011;162:818-825.

33 Green JB, Bethel MA, Paul SK, et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. *Am Heart J*. 2013;166:983-989.

34 Marx N, Rosenstock J, Kahn SE, et al. Design and baseline characteristics of the CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA®). *Diab Vasc Dis Res*. 2015;12:164-174.

35 Scirica B, Bhatt D, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317-1326.

36 Scirica BM, Braunwald E, Raz I, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation*. 2014;130:1579-1588.

37 Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet*. 2015;385:2067-2076.

Chapter 5

Guidelines and recommendations for use

Archana Dhere and Stephen CL Gough

Introduction

Incretin-based therapies now play an important role in the treatment of type 2 diabetes mellitus. The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) 2015 algorithm and the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) 2015 Position Statement highlight the benefit of a patient-centered approach that encourages individualized therapy and use of medications that do not add to the disease burden, specifically with further weight gain. Most national and international guidelines such as ADA/EASD 2015, AACE/ACE 2015, International Diabetes Federation (IDF) 2012, and the National Institute for Health and Care Excellence (NICE) 2009 (currently being updated) recognize the role of incretin-based therapies; however, the recommendations vary based on geographical availability and local prescribing costs.

American Association of Clinical Endocrinologists/ American College of Endocrinology

The 2015 AACE/ACE guidelines have incorporated body mass index (BMI) criteria, pre-diabetes, and metabolic syndrome management in a comprehensive algorithm that focuses on weight loss and prevention of development of overt type 2 diabetes mellitus (Figure 5.1) [1,2].

S. Gough (ed.), *Handbook of Incretin-based Therapies in Type 2 Diabetes*, DOI 10.1007/978-3-319-08982-9_5

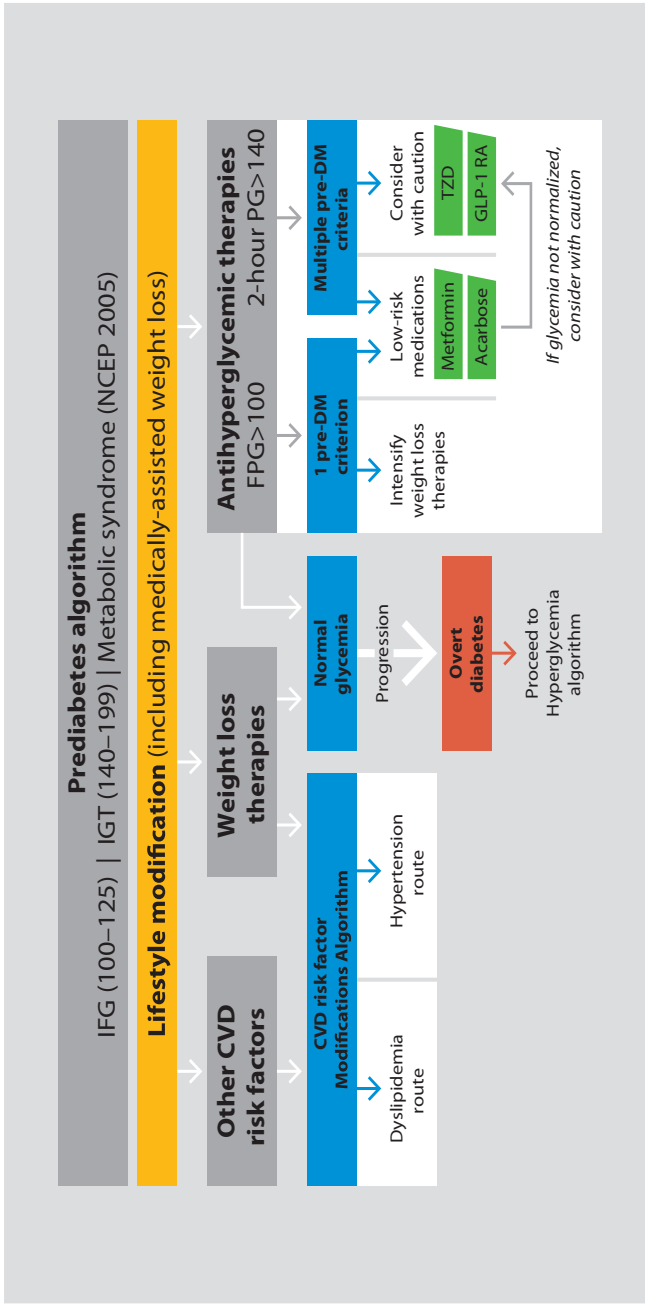

Figure 5.1 The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) 2015 algorithm for management of pre-diabetes and metabolic syndrome. CVD, cardiovascular disease; DM, diabetes mellitus; FPG, fasting plasma glucose; GLP-1 RA, glucagon- like peptide 1 receptor agonist; IFG, impaired fasting glucose. IGT, impaired glucose tolerance; PD, pre-diabetes; PG, post-prandial glucose; TZD, thiazolidinediones; Figure adapted with permission from AACE/ACE [1] ©ACCE/ACE.

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are recognized as important agents to be used alongside metformin and acarbose at the pre-diabetes stage. The AACE/ACE guideline encourages strict glycemic control, recommending a target HbA1c <6.5% (47.5 mmol/mol), fasting plasma glucose <110 mg/dL (6.1 mmol/L), and 2-hour post-prandial glucose <140 mg/dL (<7.7 mmol/L) once type 2 diabetes mellitus is established, particularly in the early stages. In longer standing diabetes associated with comorbidities and serious hypoglycemia, the treatment targets are somewhat relaxed to 7–8% (53–63 mmol/mol). All agents associated with less risk for hypoglycemia and weight gain including metformin, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 RAs, and SGLT2 inhibitors are recommended as preferred options when compared to glinides and sulphonylureas to reduce undesirable side effects (Figure 5.2).

At the first presentation of diabetes, if HbA1c is <7.5% (58 mmol/mol), GLP-1 RAs or DPP-4 inhibitors can be used as first line monotherapy, in a similar manner to metformin, sodium glucose co-transporter 2 (SGLT2) inhibitors and acarbose. If HbA1c >7.5% (>58 mmol/mol), GLP-1 RAs or DPP-4 inhibitors can be used in combination with metformin or other agents as dual therapy. If HbA1c is >9% (75 mmol/mol) at presentation, combining GLP-1 RA or DPP-4 inhibitor with metformin and insulin as triple therapy may be beneficial.

If patients have symptoms of hyperglycemia with a high HbA1c, insulin should be considered in combination with or without oral agents and GLP-1 RAs. Amongst the incretin-based drugs, GLP-1 RAs are generally the preferred option after metformin for monotherapy, dual and triple therapy, as they are more efficacious in terms of HbA1c reduction and weight loss [1].

As demonstrated in previous chapters, incretin-based therapies, along with, for example, SGLT2 inhibitors, have been shown to significantly reduce post-prandial blood glucose levels. GLP-1 RAs and DPP-4 inhibitors are specifically recommended as an alternative to prandial insulin if prandial control is suboptimal with basal insulin monotherapy [1].

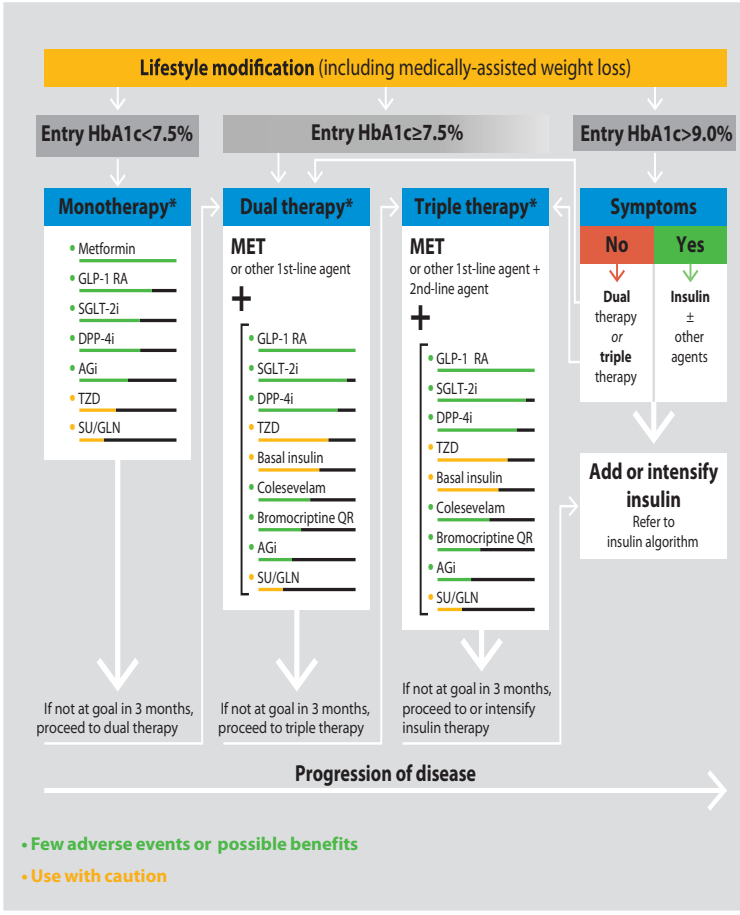

Figure 5.2 The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) 2015 algorithm for the glycemic management of type 2 diabetes mellitus. AGi, alpha glucosidase inhibitors; DPP-4i, dipeptidyl peptidase 4 inhibitors; GLN, glinides; GLP-1 RA, glucagon- like peptide 1 receptor agonist; QR, quick release; SGLT-2i, sodium- glucose cotransporter 2 inhibitors; SU, sulphonylureas; TZD, thiazolidinediones. *Order of medications listed represents suggested hierarchy of usage. Figure adapted with permission from AACE/ACE [2] ©ACCE/ACE.

Additionally, incretin-based agents are recommended by AACE/ACE due to their low potential for hypoglycemia, weight neutrality, and potential to cause weight loss [1].

American Diabetes Association/European Association for Study of Diabetes

In the 2015 ADA/EASD position statement update, GLP-1 RAs and DPP-4 inhibitors, along with sulphonylureas, rapid-acting secretagogues (glinides), thiazolidinediones, and SGLT2 inhibitors, are recommended as alternatives to metformin monotherapy if there is an intolerance, or as add-on second-line agents if blood glucose is suboptimal (Figure 5.3) [3].

The ADA/EASD guidelines do not prioritize one agent over another but do provide advice on patient factors that may help the clinician choose which class of therapy might be best suited to the patient. Cellular mechanisms, primary physiological actions, and the clinical advantages and disadvantages of each drug class are also highlighted.

The ADA/EASD target goals are less specific than those recommended in the AACE/ACE guideline; an HbA1c target of 7% (53.0 mmol/mol) is used but it is highlighted that this is only meant to "provide some context to the recommendations regarding stringency of treatment efforts," and target goals should be individualized (Figure 5.4).

As with the AACE/ACE guideline, the emphasis of the position statement is very much on individualized care in terms of HbA1c target and therapy selection. In context of GLP-1 RAs, they are recommended as an alternative to metformin in some patients and as add-on to other oral therapies, as well as in combination with a basal insulin as an alternative to meal-time insulin (combination injectable therapy).

International Diabetes Federation

The most recent IDF guidelines were published in 2012 and the recommended blood glucose goals are similar to ADA/EASD guidelines [4]:

- HbA1c <7.0% (53 mmol/mol);
- fasting glucose <115 mg/dL (6.5 mmol/L); and
- 2-hour post-prandial glucose <160 g/dL (<9.0 mmol/L).

The guidelines suggest that a lower HbA1c target may be considered if it is safe to do so and a higher level should be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia. The guidelines suggest these targets should be reviewed regularly [4].

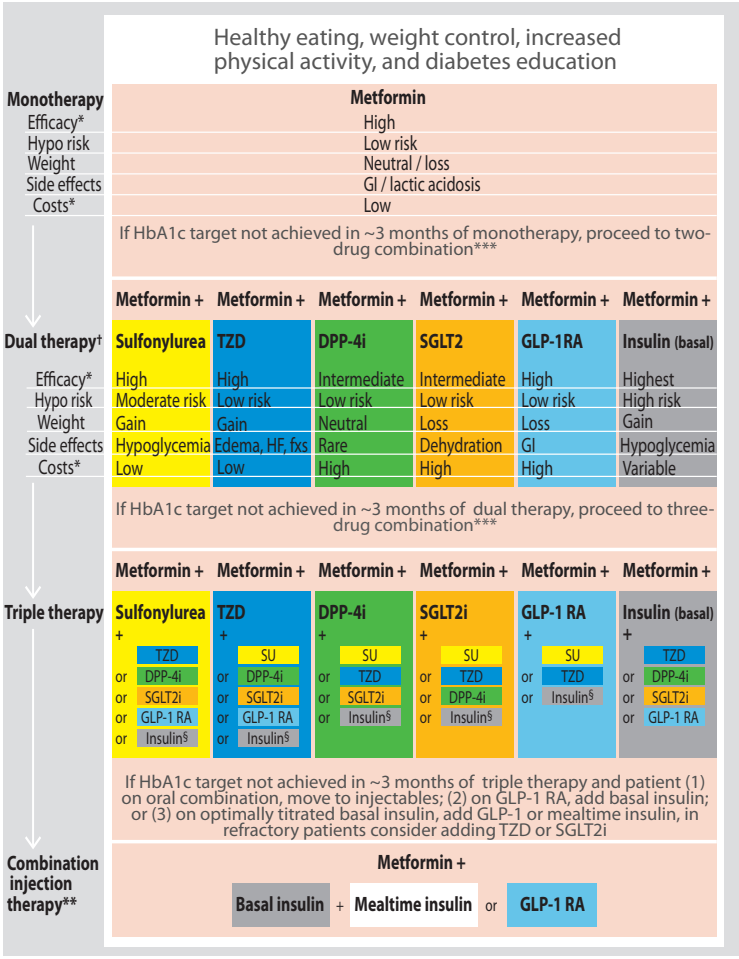

Figure 5.3 General recommendations on glucose management from the American Diabetes Association/European Association for the Study of Diabetes 2015 position statements. DPP-4i, dipeptidyl peptidase 4 inhibitors; GI, gastrointerstinal; GLP-1 RA, glucagon-like peptide 1 receptor agonist; GU, genitourinary; SGLT-2i, sodium- glucose cotransporter 2 inhibitors; SU, sulphonylureas; TZD, thiazolidinediones. †Consider initial therapy at this stage when HbA1c is ≥9% (≥75 mmol/mol). **Consider initial therapy at this stage when blood glucose is ≥300–350 mg/dL (≥16.7–19.4 mmol/L) and/or HbA1c ≥10–12% (≥86–108 mmol/mol), especially if patient is symptomatic or if catabolic features (weight loss, ketosis) are present, in which case basal insulin + mealtime insulin is the preferred initial regimen. ***Order not meant to denote any specific preference - choice dependent on variety of patient and disease-specific factors. §Usually a basal insulin (eg, NPH, glargine, detemir, degludec). Figure adapted with permission from Inzucchi et al [3] ©ADA.

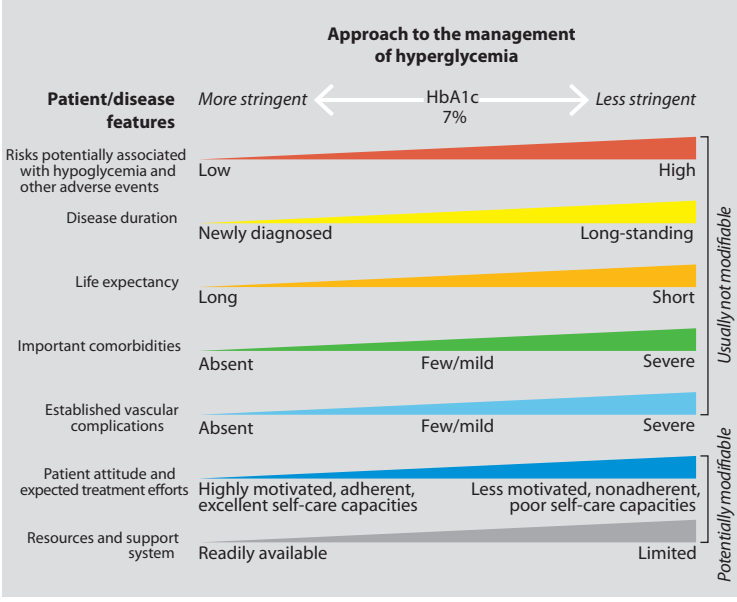

Figure 5.4 Patient and disease features that may be taken into account when individualizing management and patient-focused glycemic target. Figure adapted with permission from Inzucchi et al [3] ©ADA.

As shown in Figure 5.5, DPP-4 inhibitors are to be considered second-line as an 'alternative approach,' after metformin, sulphonylurea, and an alpha glucosidase inhibitor, or third-line 'usual approach.' GLP-1 RAs are only included as a third-line 'alternative approach.' While recognizing the existence of ongoing studies, the IDF global guidance suggests that both DPP-4 inhibitors and GLP1 RAs are relatively expensive in many countries and there is a lack of long-term outcome data.

National Institute of Health and Care Excellence

The currently available NICE guidance was published in 2009 and is undergoing major revision at the time of writing [5,6]. The 2009 guidance recommends GLP-1 RAs or DPP-4 inhibitors as alternative agents and predominantly as add-on therapy (eg, second- or third-line agents) if intolerance to metformin, sulphonylureas, or failure to achieve a glycemic target on traditional oral antihyperglycemic agents (Figure 5.6).

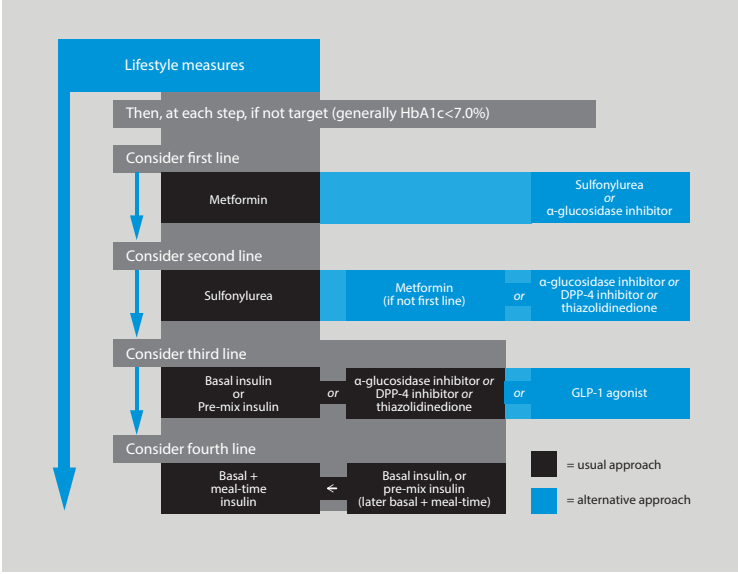

Figure 5.5 International Diabetes Federation (IDF) 2012 treatment algorithm for type 2 diabetes. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1 [4] ©IDF.

NICE identifies a specific role for DPP-4 inhibitors in high-risk jobs such as heavy goods vehicle (HGV) drivers and the elderly, where hypoglycemia can be particularly problematic. DPP-4 inhibitors are recommended instead of sulphonylureas in these special circumstances or if there is intolerance to sulphonylureas. DPP-4 inhibitors are also recommended as a third-line agent if the HbA1c is >7.5% in spite of metformin and sulphonylureas and insulin is unacceptable to the patient. NICE encourages a review of therapeutic response after 6 months and suggests stopping DPP-4 inhibitors if reduction in HbA1c is not at least 0.5%.

GLP-1 RAs are only recommended as third-line agents if the HbA1c is >7.5% on metformin and sulphonylureas in patients with a BMI>35 or associated psychological or medical implications of being overweight and if BMI<35 and insulin therapy has occupational implications or weight loss would benefit obesity related comorbidities. The guidance also suggests that GLP-1 RAs should be continued only if adequate metabolic response in the form of reduction in HbA1c by 1% and weight loss of at least 3% of initial body weight in 6 months.

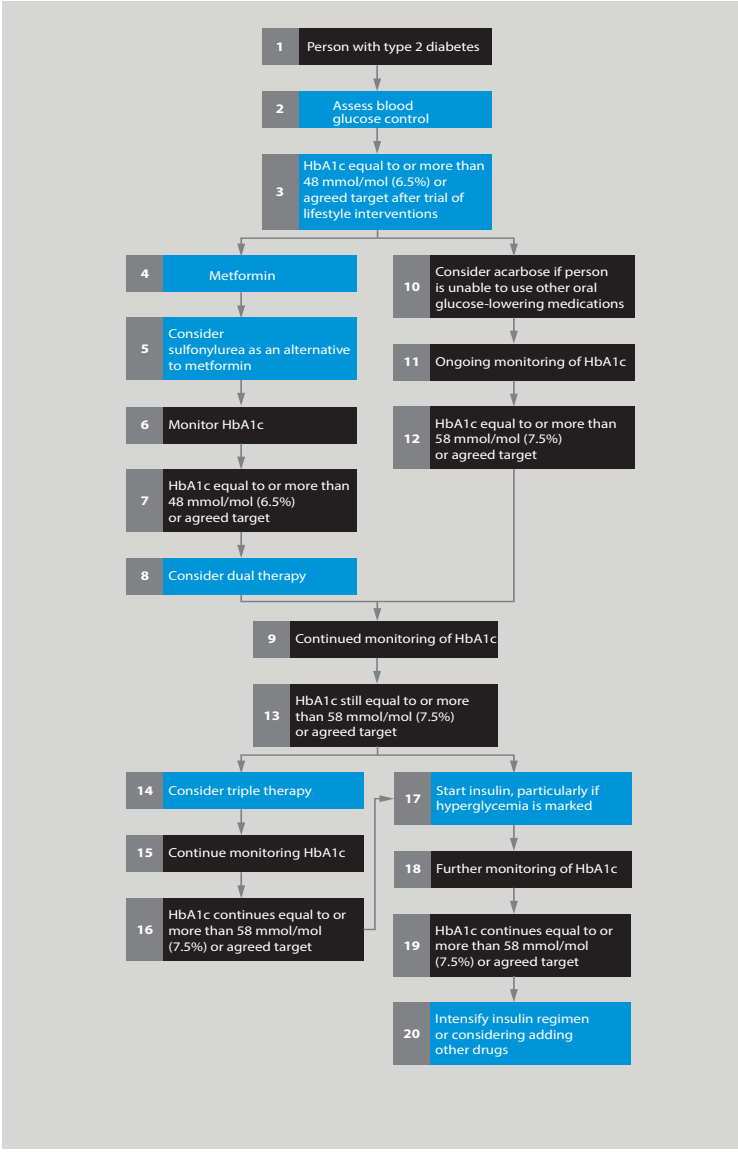

Figure 5.6 National Institute for Health and Care Excellence (NICE) blood-glucose-lowering therapy for type 2 diabetes. For in-depth guidance regarding combination therapies, visit http://pathways.nice.org.uk/pathways/diabetes. Reproduced with permission from NICE [6] ©NICE.

The recently released draft guidance indicates that NICE will suggest that for adults with type 2 diabetes, clinicians should discuss the benefits and risks of drug treatment, and the options available (Figure 5.6). The choice of an individual therapy should be based upon the effectiveness of the drug treatment in terms of metabolic response, safety, and tolerability of the drug treatment, the person's individual clinical circumstances, (including comorbidities and risks from polypharmacy), individual patient preferences and needs, licensed indications or combinations available, and cost, endorsing the choice of lowest acquisition cost.

Whilst metformin should be considered as first line, DPP-4 inhibitors can be used first-line in metformin intolerance or as second-line alongside pioglitazone, repaglinide, or a sulphonylurea. All of these oral agents can be considered in triple therapy for patients not controlled on dual therapy. GLP-1 RAs should be considered if triple oral therapy fails in patients satisfying the previously mentioned BMI criteria; the discontinuation criteria should also be considered. GLP1 RAs should only be used in combination with insulin following specialist care advice and ongoing support (for example, from a diabetologist or GP with a special interest in diabetes).

Using incretin-based therapies in clinical practice

Although there appear to be some differences between the individual guidelines and position statements, all major guidelines now recognise the importance of incretin-based therapies in the management of people with type 2 diabetes at all stages of the disease continuum. With all the guidance provided, there is an increasing focus on an individualized patient-centered approach in which the clinical profile of the patient should, wherever possible, be matched to the pharmacological characteristics of the drug to achieve maximum benefit with minimal unwanted side effects. With respect to incretin-based therapies, specific consideration

is given to their beneficial effects on glycemic control with a low risk of hypoglycemia, weight neutrality with DPP-4 inhibitors, and weight loss with the GLP-1 RAs.

DPP-4 inhibitors are currently once-daily oral therapies and GLP-1 RAs are currently avilable in twice-daily, once-daily, and once-weekly injectable doses. These different modes and frequencies of administration will be important for deciding the most appropriate treatment in certain patients.

Some of the guidelines and position statements do not just refer to the classes of incretin-based therapies (ie, DPP-4 inhibitors and the GLP-1 RAs) but individual drug names, especially as more data become available from large long-term safety studies. Rightly or wrongly, some specific therapies are recommended based upon drug acquisition costs rather than long-term diabetes care costs.

In addition to the use of incretin-based therapies as mono-, dual, triple therapy, and in combination with insulin, fixed ratio combinations of oral agents (eg, metformin with DPP-4 inhibitors) and injectable therapies (eg, basal insulin with a GLP-1 RA) are now being licensed. These are likely to feature in guidance updates in the future.

Ultimately, the decision to use incretin-based therapies and the selection of a specific drug will be down to the healthcare professional and may be largely driven by the guideline or position statement endorsed by the local formulary and payers.

Availability and licences

The currently licensed DPP-4 inhibitors and GLP-1 RAs are listed in Tables 5.1 and 5.2 [7–36]. The table shows license availability in the UK, Europe, and the USA; use with respect to mono-, dual, and triple therapy; use with insulin; use in hepatic and renal impairment; and the availability of long-term safety data.

Therapy [Refs]	Mono therapy	Dual MET	Dual SU	Dual PIO	Dual and triple insulin	Triple MET + SU	CVS safety studies	Renal impairment dose adjustment	Hepatic impairment dose adjustment	EU /UK license	USA license
Sitagliptin [7–9]	Yes	Yes	Yes	Yes	Yes	Yes	TECOS	Yes	No	Yes	Yes
Saxagliptin [10–12]	Yes	Yes	Yes	Yes	Yes	No	SAVOR TIMI 53	Yes	No	Yes	Yes
Alogliptin [13–15]	Yes	Yes	Yes	Yes	No	Yes	EXAMINE	Yes	No	Yes	Yes
Vilda-gliptin [16,17]	Yes	Yes	Yes	Yes	Yes	No	VIVIDD	Yes	C/I	Yes	No
Linagliptin [18–20]	Yes	Yes	Yes	No	Yes	No	CAROLINA	No	No	Yes	Yes

Table 5.1 Currently licenced DPP-4 inhibitors. C/I, contraindicated; CVS, cardiovascular system; MET, metformin; PIO, pioglitazone; SU, sulphonylurea.

	Mono therapy	Dual MET	Dual SU	Dual PIO	Dual and triple insulin	Triple MET + SU	Triple MET + PIO	CVS safety studies	Renal impairment dose adjustment	Hepatic impairment dose adjustment	EU/UK license	USA license
Exenatide [21–23]	Yes (in Europe)	Yes	Yes	Yes	Yes	Yes	Yes	EXSCEL	Caution in severe RI	No	Yes	Yes
Lixisenatide [24,25]	No	Yes	Yes	Yes	Yes	Yes	Yes	ELIXA	Caution in severe RI	No	Yes	Yes
Liraglutide [26–28]	No	Yes	Yes	Yes	No	Yes	Yes	LEADER	Dose reduction in severe RI	No	Yes	Yes
Exenatide QW [29–31]	No	Yes	Yes		Yes	Yes	Yes	EXSCEL	Caution in severe RI	No	Yes	No
Dulaglutide [32–34]	Yes (in Europe)	Yes	Yes	Yes	Yes	Yes	Yes	REWIND	Caution in severe RI	No	Yes	Yes
Albiglutide [35,36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NCT 02465515	Caution in severe RI	No	Yes (No in UK)	Yes

Table 5.2 Currently licenced GLP-1 RAs. CVS, cardiovascular system; MET, metformin; PIO, pioglitazone; SU, sulphonylurea.

References

1. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology – clinical practice guidelines for developing a diabetes mellitus comprehensive care plan – 2015 Executive Summary. *Endocr Pract*. 2015;21:413-437.
2. Garber A, Abrahamson MJ, Brazilay JI, Blonde L, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive diabetes management algorithm 2015. *Endoc Pract.* 2015; 21: 438-447.
3. Inzucchi SE, Berganstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centered approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140-149.
4. International Diabetes Federation (IDF). IDF Clinical Guidelines (2011/2012): Global Guidelines for Type 2 Diabetes. www.idf.org/guidelines. Accessed October 10, 2015.
5. National Institute for Health and Care Excellence (NICE). Type 2 diabetes: the management of type 2 diabetes (2009): Clinical Guideline 87. www.nice.org.uk/guidance/cg87. Accessed October 10, 2015.
6. National Institute for Health and Care Excellence (NICE). Blood-glucose lowering therapy in type 2 diabetes. http://pathways.nice.org.uk/pathways/diabetes/blood-glucose-lowering therapy-for-type-2-diabetes.xml. Accessed October 10, 2015.
7. Electronic Medicines Compendium. Januvia SPC. www.medicines.org.uk/emc/medicine/19609/SPC. Accessed October 10, 2015.
8. European Medicines Agency. Summary of Product Characteristics. Januvia 25 mg. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000722/WC500039054.pdf. Accessed October 10, 2015.
9. Food and Drug Administration (FDA). Highlights of prescibing information. Januvia (sitagliptin). www.accessdata.fda.gov/drugsatfda_docs/label/2015/021995s033lbl.pdf. Updated March 2015. Accessed October 10, 2015.
10. Electronic Medicines Compendium. Onglyza SPC. www.medicines.org.uk/emc/medicine/22315/SPC. Accessed October 10, 2015.
11. European Medicines Agency. Summary of Product Characteristics. Onglyza 2.5 mg. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001039/WC500044316.pdf. Accessed October 10, 2015.
12. Food and Drug Administration (FDA). Highlights of prescibing information. Onglyza (saxagliptin). www.accessdata.fda.gov/drugsatfda_docs/label/2013/022350s011lbl.pdf. Updated May 2013. Accessed August 10, 2015.
13. Electronic Medicines Compendium. Vipidia SPC. www.medicines.org.uk/emc/medicine/28513/SPC. Accessed August 10, 2015.
14. European Medicines Agency. Summary of Product Characteristics. Vipidia 6.25. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002182/WC500152271.pdf. Accessed August 10, 2015.
15. Food and Drug Administration (FDA). Highlights of prescibing information. Vipidia (alogliptin). www.accessdata.fda.gov/drugsatfda_docs/label/2013/022271s000lbl.pdf. Updated January 2013. Accessed October 10, 2015.
16. Electronic Medicines Compendium. Galvus SPC. www.medicines.org.uk/emc/medicine/20734/SPC. Accessed October 10, 2015.
17. European Medicines Agency. Summary of product characteristics. Galvus 50 mg. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000771/WC500020327.pdf. Accessed October 10, 2015.
18. Electronic Medicines Compendium. Trajenta SPC. www.medicines.org.uk/emc/medicine/25000/SPC. Accessed October 10, 2015.

19. European Medicines Agency. Summary of product characteristics. Trajenta 5 mg. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002110/WC500115745.pdf. Accessed October 10, 2015.
20. Food and Drug Administration. Highlights of prescibing information. Tradjenta (linagliptin). www.accessdata.fda.gov/drugsatfda_docs/label/2015/201280s011lbl.pdf. Updated July 2015. Accessed October 10, 2015.
21. Electronic Medicines Compendium. Byetta SPC. www.medicines.org.uk/emc/medicine/19257. Accessed October 10, 2015.
22. European Medicines Agency. Summary of product characteristics. Byetta 5 µg. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000698/WC500051845.pdf. Accessed October 10, 2015.
23. Food and Drug Administration (FDA). Highlights of prescribing information. Byetta (exenatide). www.accessdata.fda.gov/drugsatfda_docs/label/2015/021773s040lbl.pdf. Updated February 2015. Accessed October 10, 2015.
24. Electronic Medicines Compendium. Lyxumia SPC. www.medicines.org.uk/emc/medicine/27405. Accessed October 10, 2015.
25. European Medicines Agency. Summary of product characteristics. Lyxumia 10 µg. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002445/WC500140401.pdf. Accessed October 10, 2015.
26. Electronic Medicines Compendium. Victoza SPC. www.medicines.org.uk/emc/medicine/21986. Accessed October 10, 2015.
27. European Medicines Agency. Summary of product characteristics. Victoza 6 mg/ml. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf. Accessed October 10, 2015.
28. Food and Drug Administration (FDA). Highlights of prescribing information. Victoza (liraglutide). www.accessdata.fda.gov/drugsatfda_docs/label/2015/022341s023lbl.pdf. Updated March 2015. Accessed October 10, 2015.
29. Electronic Medicines Compendium. Bydureon SPC. www.medicines.org.uk/emc/medicine/24665. Accessed October 10, 2015.
30. European Medicines Agency. Summary of product characteristics. Bydureon 2mg. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002020/WC500108241.pdf. Accessed October 10, 2015.
31. Food and Drug Administration (FDA). Highlights of prescribing information. Bydueron (exenatide extended release). www.accessdata.fda.gov/drugsatfda_docs/label/2015/022200s019lbl.pdf. Accessed October 10, 2015.
32. Electronic Medicines Compendium. Trulicity SPC. www.medicines.org.uk/emc/medicine/29747. Accessed October 10, 2015.
33. European Medicines Agency. Summary of product characteristics. Trulicity 0.75mg. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002825/WC500179470.pdf. Accessed October 10, 2015.
34. Food and Drug Administration (FDA). Highlights of prescribing information. Trulicity (dulaglutide). www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000Lbl.pdf. Updated Sept 2014. Accessed October 10, 2015.
35. European Medicines Agency. Summary of product characteristics. Eperzan 30 mg. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002735/WC500165117.pdf. Accessed October 10, 2015.
36. Food and Drug Administration. Highlights of prescribing information. Tanzeum (albiglutide). www.accessdata.fda.gov/drugsatfda_docs/label/2015/125431s009lbl.pdf. Updated May 2015. Accessed October 10, 2015.

Chapter 6

Future and emerging therapies

Eduard Montanya

Introduction

This chapter is focused on investigational drugs, new methods of administration, and potential new indications of glucagon-like peptide-1 (GLP-1)-based therapies.

Once-weekly agents under investigation

Dulaglutide

Dulaglutide is a long-acting human GLP-1 receptor agonist (GLP-1 RA) developed for once-weekly administration. The molecule has two identical disulphide-linked chains, each containing an N-terminal GLP-1 analogue sequence covalently linked to a modified human immunoglobulin G4 heavy chain by a small peptide linker [1]. The large size of dulaglutide slows absorption and reduces renal clearance, and the molecular characteristics result in a soluble formulation with a half-life of approximately 5 days that makes it suitable for weekly subcutaneous administration. Peak activity of dulaglutide takes place 12–72 hours after administration and steady state is reached after 2 or 3 weeks [2].

The Phase III randomized Assessment of Weekly AdministRation of LY2189265 (dulaglutide) in Diabetes (AWARD) clinical trial program, comprising six trials, evaluated the efficacy and safety of dulaglutide [3–8]. The AWARD-5 trial included an initial dose-finding portion exploring seven doses (0.25, 0.50, 0.75, 1.0, 1.5, 2.0, and 3.0 mg), concluding that 1.5 mg is the dose with the highest posterior probability of being the maximum utility dose [7]. Dulaglutide 0.75 mg met the criteria for a lower dose in

S. Gough (ed.), *Handbook of Incretin-based Therapies in Type 2 Diabetes*, DOI 10.1007/978-3-319-08982-9_6

case of an observed unforeseen safety signal with the optimal dose during subsequent clinical development [9]. This selection was also supported by pharmacokinetic/pharmacodynamic (PK/PD) model-based analysis and by subsequent results of the efficacy and safety assessment up to 104 weeks. Thus, 1.5 mg and 0.75 mg doses were selected for further clinical development.

A summary of the main characteristics and efficacy results (blood sugar control and body weight reduction) of all six AWARD trials is provided in Table 6.1 [3–8]. In addition, dulaglutide 1.5 mg showed modest beneficial effects on lipid profile in AWARD-4 trial [6], with a decrease in LDL cholesterol and significant between treatment difference versus sitagliptin, and in AWARD-1 trial [3] with significant reductions in total and LDL cholesterol values compared with placebo and in triglyceride levels compared with exenatide. Compared with other GLP-1 based therapies, the incidence of total hypoglycemia was 10.2%, 5.3%, and 4.8% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and sitagliptin respectively (AWARD-4) and significantly fewer patients experienced hypoglycemia in the dulaglutide 1.5 mg arm (10.4%) compared with the exenatide arm (15.9%) in AWARD-1 [3,6]. In summary, dulaglutide has shown superior HbA1c reductions than comparators in AWARD 1–5 trials (metformin, glargine, sitagliptin and exenatide), and is the only GLP-1 analogue that has shown noninferiority to liraglutide in HbA1c reduction, even though body weight reduction was lower with dulaglutide (AWARD-6) [6]. Dulaglutide has shown a favorable body weight profile and no increased hypoglycemic event rates. Modest reductions in LDL cholesterol have been observed in some of the trials with dulaglutide 1.5mg [3,6].

The safety profile of dulaglutide in the AWARD Phase III clinical trials has generally been consistent with the known effects of the GLP-1 RA class. Patients treated with dulaglutide have reported an increased incidence of gastrointestinal adverse events, similar to those of exenatide [3–8]. An increase in heart rate has been consistently found in the 1–3 beats/minute range [3,5,7,8]. Increased levels of total amylases, pancreatic amylases, and lipases have been found with both doses of dulaglutide in the trials. For dulaglutide 1.5 mg, the increase in total and pancreatic amylases was higher than with sitagliptin (AWARD-5)

Trial	Duration (weeks)	Background therapy	Comparator	Mean baseline HbA1c (%)	Change in HbA1c (%) dulaglutide 1.5 mg	Change in HbA1c (%) dulaglutide 0.75 mg	Change in HbA1c (%) comparator	Change in body weight (kg) dulaglutide 1.5 mg	Change in body weight (kg) dulaglutide 0.75 mg	Change in body weight (kg) comparator
AWARD-1 [3]	26	metformin + pioglitazone	exenatide or placebo	8.1±1.3	−1.51±0.06	−1.30±0.06	exenatide: −0.99±0.06 placebo: −0.45±0.08	−1.30±0.29	0.20±0.29	exenatide: −1.27±0.29 placebo: 1.24±0.37
AWARD-2 [4]	52	metformin + glimepiride	insulin glargine	----	−1.08	Non-inferior	−0.63	−1.87	Reduced	1.44
AWARD-3 [5]	52	----	metformin	7.6±0.9	−0.78±0.06	−0.71±0.06	−0.56±0.06	−2.29±0.24	-1.36±0.24	−2.22±0.24
AWARD-4 [6]	52	mealtime insulin lispro ± metformin	insulin glargine	8.5	−1.48±0.08	−1.42±0.08	−1.23±0.08	−0.35±0.34	0.86±0.33	2.89±0.33
AWARD-5 [7]	52	metformin	sitagliptin	8.1±1.1	−1.10±0.06	−0.87±0.06	−0.39±0.06	−3.03±0.22	−2.60±0.23	−1.53±0.24
AWARD-6 [8]	26	metformin	liraglutide	----	−1.42±0.05	----	−1.36±0.06	−2.9	----	−3.6

Table6.1. Dulaglutide clinical trial program (AWARD) in type 2 diabetes. HbA1c, glycated hemoglobin.

and exenatide (AWARD-1) [3,7]. As in Phase III clinical trials for other GLP-1 RAs, pancreatitis occurred in few patients in dulaglutide and comparator arms, but the number of episodes was insufficient to make meaningful comparisons.

Dulaglutide immunogenicity has also been explored in this Phase III program [3,5,7,8]. Few patients (≤2%) developed treatment-emergent dulaglutide antidrug antibodies; 22–60% of them were neutralizing antibodies. No systemic hypersensitivity events have been reported, and injection site reactions have been rare.

Semaglutide

Semaglutide is a long-acting acylated human GLP-1 RA in development for once-weekly administration. The PK/PD of semaglutide have been explored in a single-dose, dose escalation trial with seven doses ranging from 0.625–20 μg/kg given to healthy males [10]. The maximum tolerated single dose was 15 μg/kg body weight. Plasma mean elimination half-life was 155–173 hours and mean t_{max} 16–20 hours, a profile compatible with once-weekly administration. No safety concerns were identified in the trial. Dose response of once-weekly semaglutide has been investigated in subjects with type 2 diabetes (TD2) [11]. The safety and pharmacodynamics of semaglutide were also investigated and compared with placebo and daily liraglutide in a 12-week randomized, double-blind, placebo-controlled trial. Semaglutide dose dependently reduced HbA1c for doses ≥0.2 mg, and body weight for doses ≥0.8 mg (up to 4.8 kg vs 1.2 kg with placebo) [11].

Treatment with semaglutide ≥0.8 mg was found to be more effective than liraglutide 1.8 mg, but withdrawals due to gastrointestinal adverse events were also higher with higher doses of semaglutide (liraglutide 1.8 mg: 10%; semaglutide 0.8 mg: 14.3%; semaglutide 1.6 mg: 27.7%) [11]. There were few episodes of hypoglycemia with liraglutide and semaglutide [11]. Injection site reactions were uncommon and similar with liraglutide and semaglutide. Only one subject treated with semaglutide (1.6 mg) developed low-titer anti-semaglutide antibodies that were non-neutralizing. No safety concerns were identified in the trial.

The pharmacokinetics and tolerability of a single dose of 0.5 mg of semaglutide in nondiabetic subjects, with and without renal impairment, have been recently reported [12]. In patients with mild and moderate renal impairment and end-stage renal disease (ESRD) groups, the exposure to semaglutide was similar to that in healthy subjects, but in the ESRD group, mean semaglutide exposure was 22% higher than in healthy subjects [12]. Tolerance to semaglutide was similar in patients with and without renal impairment. Thus, the results of this small single-dose trial suggests that adjustment of semaglutide dose may not be required in subjects with renal impairment, but the long-term effect of semaglutide in these patients needs additional investigation.

Subcutaneous implants

ITCA 650 is a miniature osmotic pump system that delivers continuous subcutaneous release of exenatide in low and continuous amounts at specified doses (Figure 6.1). The pump is the size of a small match stick, can be inserted via an in-office procedure, and removal requires a small (~5 mm) incision. The system achieves rapid, steady state delivery of exenatide upon insertion and, if required, the removal of the device results in prompt absence of exenatide in the body within hours. The pump is designed to deliver exenatide for up to 12 months with a single placement, even though in published trials, it has not been in place for more than 3 months [13,14].

PK/PD assessment of continuous subcutaneous delivery of exenatide in subjects with TD2 has been investigated in a 28-day Phase Ib study [13] and a 24-week Phase II study [14]. ITCA 650 doses ranged from 10–80 μg/day and from 20–80 μg/day in Phase Ib and Phase II trials, respectively. Plasma levels of exenatide were detected in 75% of

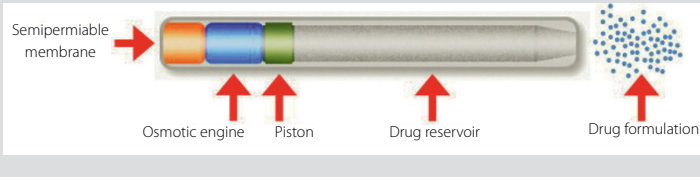

Figure 6.1 Schematic representation of ITCA 650 miniature osmotic pump system. ITCA 650 delivers continuous subcutaneous release of exenatide in low and continuous amounts at specified doses. Reproduced with permission from Henry et al [13]©Elsevier.

subjects within 6–12 hours of insertion, steady state concentrations were achieved within 24–48 hours, and exenatide was not measurable in any subject 24 hours after ITCA 650 removal [13]. Plasma glucose (fasting and postprandial) decreased significantly in the ≥20μg/day dose groups within 1–5 days of ITCA 650 insertion [13].

In the aforementioned Phase II study, all doses (20–80μg/day) were active suggesting an ED_{50} of <20μg/day [14]. Higher exenatide doses tended to produce larger reductions in HbA1c and body weight, with 86% of subjects experiencing weight loss [14]. Those given 20μg/day as initial dose resulted in less overall nausea than the 40μg/day dose, and the subsequent increment to 60μg/day produced similar reductions in HbA1c, but was better tolerated than the 80μg/day dose. Thus, the 20–60μg/day dose sequence was considered the best strategy for further examination in Phase III trials.

The 24-week extension of this trial has shown maintenance of the changes in HbA1c, body weight, and fasting plasma glucose at week 48 [15]. Approximately 50% of patients reported adverse local reactions at the incision site but no patients were terminated from study due to local adverse events. Patient satisfaction with ITCA 650 resulted in substantially greater improvements in quality of life (QOL) scores when compared with exenatide twice-daily, particularly with respect to lifestyle and convenience sub-scales [16]. Patients initially treated with exenatide twice-daily had substantial improvements in treatment satisfaction (as measured by a Diabetes Satisfaction Tool consisting of 16 questions and evaluating overall satisfaction, as well as satisfaction grouped in four subscales) when they switched to ITCA 650 [16].

The ongoing FREEDOM Phase III trial seeks to determine the tolerability and efficacy of once- or twice-yearly dosing of ITCA 650 [17]. The potential of ITCA 650 to ensure 100% adherence to treatment provides new opportunities to improve long-term outcomes. In terms of safety, the rapid reduction of exenatide concentrations upon ITCA 650 removal is a potential advantage if adverse events such as pancreatitis occur.

Oral GLP-1 receptor agonists

Oral GLP-1 receptor agonists are now in early clinical development. The oral exenatide ORMD-0901 is in Phase II clinical trials and an oral insulin (ORMD-0801)/oral exenatide (ORMD-0901) fixed-dose combination tablet is in preclinical development.

A sustained-release oral version of semaglutide (NN-9928) is currently undergoing Phase I testing and oral semaglutide (NN-9924) has completed Phase I testing; Phase II is ongoing. Oral GLP-1 (doses of 0.5, 1.0, 2.0, and 4.0 mg) has been given to six healthy male subjects [18] as a single tablet and induced a dose-dependent increase in plasma drug concentration and on insulin release, showing that oral GLP-1 was active. The higher doses of oral GLP-1 induced nausea, as described in patients treated with injectable GLP-1 [18].

Fixed-dose combinations with insulin therapy

GLP-1 RA and insulin have complementary effects and a combination of these agents can be used to intensify antihyperglycemic therapy, while minimizing unwanted effects. The combination has been explored in several clinical trials and is now commonly used in clinical practice [19]. A new strategy using fixed-ratio combinations of basal insulin and GLP-1 agonist is now in clinical development. For example, a fixed-dose combination of insulin degludec and liraglutide (IDegLira) has been studied in two 26-week Phase III clinical trials (DUAL-I and DUAL-II) in patients with T2D [20–22]. In DUAL-I, patients uncontrolled on metformin with or without pioglitazone were randomized to receive IDegLira, insulin degludec, or liraglutide. The mean HbA1c reduction in IDegLira group (–1.8%; from 8.3% to 6.4%) was superior to liraglutide (–1.3%) and noninferior to degludec (–1.4%) [20]. IDegLira resulted in a mean weight reduction of 0.5 kg and 32% lower rate of hypoglycemia than insulin degludec [20]. The 26-week extension of the trial showed the maintenance of the glucose lowering effect with HbA1c reductions from baseline of 1.8% (IDegLira), 1.4% (degludec), and 1.2% (liraglutide) [21].

In DUAL-II, patients uncontrolled on basal insulin in combination with oral antihyperglycemic agents were randomized to receive IDegLira or insulin degludec with the maximum dose of insulin degludec fixed in both treatment arms. In IDegLira group, HbA1c reduction was 1.9% (from 8.7% to 6.9%), significantly higher than that of insulin degludec (0.89%) at equivalent insulin doses [22]. Patients treated with IDegLira experienced mean weight loss of 2.7 kg, compared with no weight change with insulin [21]. Hypoglycemia incidence was comparable between the two groups (24% IDegLira; 25% insulin degludec). The gastrointestinal events were low (IDegLira vs degludec: nausea 6.5% vs. 3.5%; vomiting 3.5% vs. 0.0%), likely reflecting the slow increment in liraglutide dose with this combination [22].

A fixed-ratio combination of the GLP-1 RA lixisenatide and insulin glargine (LixiLan) is also being developed. Results of a 24-week Phase IIb study [23] in patients with T2D inadequately controlled on metformin have shown superior HbA1c reduction with LixiLan than glargine (6.3% and 6.5% respectively), with no increase in hypoglycemic events with LixiLan. Target HbA1c<7% was achieved by 84% and 78% of patients treated with LixiLan and glargine, respectively. Body weight was reduced with LixiLan, although the amounts were not disclosed [23]. The incidence of gastrointestinal side effects was low (nausea: 7.5%, vomiting 2.5%). The LixiLan Phase III development program is ongoing with two randomized clinical trials: NCT02058160 with two treatment arms comparing LixiLan and glargine with or without metformin [24]; NCT02058147 with three treatment arms comparing LixiLan, glargine, and lixisenatide in combination with metformin [25].

Investigational DPP-4 inhibitors and fixed-dose combination with SGLT2 inhibitors

Currently available DPP-4 inhibitors are administered once daily, with the exception of twice-daily vildagliptin. Longer-acting DPP-4 inhibitors intended for once-weekly administration are in development. Omarigliptin is a DPP-4 inhibitor with a pharmacokinetic profile suitable

for once-weekly dosing in human subjects that is currently in Phase III clinical development. ZYDPLA1 is in Phase I of development.

The association of DPP-4 inhibitors with the recently approved sodium glucose cotransporter 2 (SGLT2) inhibitors offers potential advantages based on complementary mechanisms of action and effects. Several combinations are currently in development. For example, a fixed-dose combination of the DPP-4 inhibitor linagliptin with the SGLT2 inhibitor empagliflozin is in Phase III development. The efficacy and safety of once-daily empagliflozin (10 mg and 25 mg) administered as oral fixed-dose combination with linagliptin (5 mg) has been compared to placebo, also in combination with linagliptin (5 mg), on metformin background therapy [26]. The same fixed-dose combination of empagliflozin and linagliptin will be compared in a randomized, double-blind, parallel-group Phase III trial in treatment-naive and metformin-treated patients [27].

A fixed-dose combination of saxagliptin and dapagliflozin is also in development. A single-dose, open-label, randomized, three-period, three-treatment, crossover Phase I trial has evaluated the pharmacokinetics of saxagliptin 5 mg and dapagliflozin 10 mg when coadministered to 42 healthy fasting subjects [28] and a Phase I trial of the fixed-dose combinations of saxagliptin (2.5 mg) + dapagliflozin (5 mg) and saxagliptin (5 mg) + dapagliflozin (10 mg) compared to the coadministration of their respective individual components has been investigated.

Other indications for incretin therapies

Obesity

The GLP-1 RA liraglutide and exenatide are being investigated as potential weight-loss therapies [29]. Liraglutide (3 mg) has been already approved as a general obesity therapy by FDA and EMA. Exenatide has been studied in a number of defined phenotypes of obesity such as Prader-Willi syndrome, hypothalamic obesity, pediatric obesity, olanzapine-induced obesity, and polycystic ovary syndrome [30,31]. GLP-1 RA may also have a role in pre-diabetes, as the proportion of patients with pre-diabetes decreased by 52% following 2 years of treatment with liraglutide in the obesity trial [32].

Type 1 diabetes

A few small studies have demonstrated beneficial effects of GLP-1 RAs when used in patients with type 1 diabetes (T1D) [33–37]. For example, addition of exenatide to insulin therapy in adolescents with T1D reduced postprandial hyperglycemia, despite reductions in insulin dose [33]. Liraglutide provided additional glycemic control when added to intensive insulin therapy in obese patients with TD1 [34] and, in a separate study, insulin doses were reduced while maintaining or further improving glycemic control [35]. Exenatide stimulated insulin secretion in T1D islet transplant recipients and allowed reduction in insulin dose for some patients [36]. The potential benefit of long-acting albiglutide in new-onset T1D is being explored in a randomized clinical trial [37].

Cardiovascular possibilities of GLP-1

GLP-1 receptors have been found in endothelial cells, vascular smooth muscle cells (VSMC), and cardiomyocytes in mice, but the distribution of the receptors in humans has not been conclusively elucidated. GLP-1 was shown to modify vascular cell growth and function, as well as the production of pro-inflammatory markers by endothelial cells. Short-term studies [38,39] using GLP-1 infusion have shown increased endothelial-dependent vasodilation and cardiomyocyte protection during ischemia and reperfusion, suggesting increased myocardial contractility in subjects with congestive heart failure.

GLP-1 RAs may exert indirect effects on the cardiovascular system based on their effects on glucose levels, body weight, blood pressure, and lipid profile. It is unknown whether these changes in cardiovascular risk factors will have a beneficial impact on clinical outcomes. GLP-1 RA have been also associated with small increments in heart rate. The bases and clinical significance of this change in heart rate have not yet been clarified. The currently ongoing trials looking specifically at cardiovascular primary outcomes in patients with TD2 treated with GLP-1-based therapies will determine the cardiovascular safety of these agents, and, if sufficiently powered, could identify potential cardiovascular benefits (Table 6.2) [40–49].

	Trial name	Study drug	*n*	Expected completion date
GLP-1s				
	ELIXA [40]	lixisenatide	~6000	Finished 2014
	LEADER [41]	liraglutide	~9300	January 2016
	EXSCEL [42]	exenatide OW	~9500	March 2017
	REWIND [43]	dulaglutide	~9600	April 2019
	FREEDOM [44]	ITCA 650 (exenatide)	~3000	August 2018
	SUSTAIN [45]	semaglutide	3260	January 2016
DPP-4 inhibitors				
	EXAMINE [46]	alogiptin	5380	Finished 2013
	SAVOR-TIMI 53 [47]	saxagliptin	16492	Finished 2013
	TECOS [48]	sitagliptin	~14000	Finished 2014
	CAROLINA [49]	linagliptin	~6000	2018

Table 6.2 Large-scale cardiovascular outcome trials of glucagon-like peptide 1 (GLP-1) analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors in type 2 diabetes.

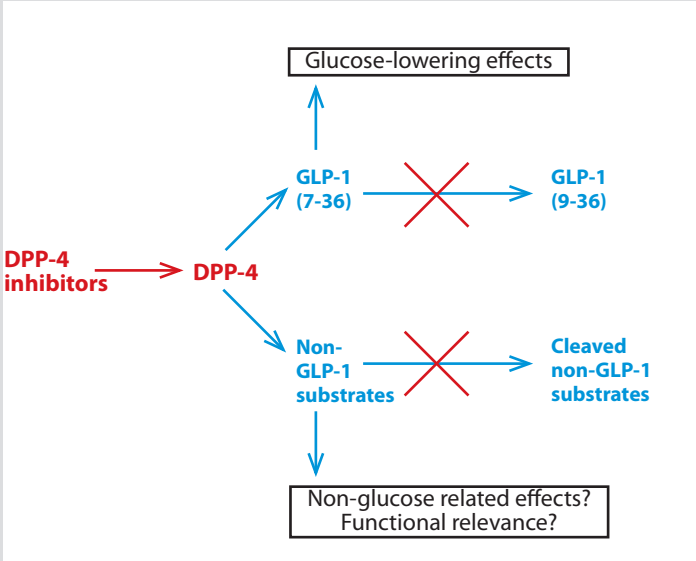

Figure 6.2 Dipeptidyl peptidase-4 (DPP-4) cleaves other substrates in addition to glucagon-like peptide 1 (GLP-1) such as neuropeptide Y and substance P, hormones (GIP), cytokines, and chemokines. The inhibition of DPP-4 may modify the concentrations these peptides and exert GLP-1-independent effects.

DPP-4 inhibitors

DPP-4 exists in two forms. The soluble form is found in the circulation and is responsible for the glucose-lowering effects of DPP-4 inhibitors. Because DPP-4 cleaves other substrates in addition to GLP-1, the inhibition of DPP-4 may modify the concentrations of these peptides and exert GLP-1-independent effects (Figure 6.2). The membrane-bound form of DPP-4 is expressed on the surface of cells such as endothelial cells, kidney tubular cells and T-cells. The ability of DPP-4 to cleave different membrane-bound substrates that interact with other membrane proteins or receptors may result in the pleiotropic effects of DPP-4 inhibition. Some of these effects may be relevant in patients with diabetes, in particular the potential action of DPP-4 on substrates with a role in cardiovascular disease or in diabetic nephropathy [50].

The expression of DPP-4 in endothelial cells is modified by glucose, hypoxia, and inflammation, and DPP-4 inhibition increases endothelial growth in vitro. DPP-4 inhibition has increased endothelial growth in vitro, and alogliptin has induced relaxation of aortic segments, an action partly dependent on nitric oxide release and not on its interaction with GLP-1 receptor. Nevertheless, these direct vascular effects, as well as those that could modify the production of inflammatory mediators involved in vascular disease, remain poorly explored.

Two cardiovascular outcome trials in patients treated with the DPP-4 inhibitors alogliptin (EXAMINE) and saxagliptin (SAVOR-TIMI) have now been published [46,47]. In both trials, the primary endpoint of cardiovascular safety versus placebo was met, although in SAVOR-TIMI, an increased risk for admission due to heart failure was identified and has prompted additional investigation [47]. As with GLP-1 RA, the results of the ongoing cardiovascular trials will provide additional information on the cardiovascular safety of DPP-4 inhibitors (Table 6.2). Meanwhile, a recent meta-analysis of randomized clinical trials with DPP-4 inhibitors including 55,141 participants has identified no cardiovascular harm, nor benefit [50].

Potential renal effects of DPP-4 inhibitors

Membrane-bound DPP-4 is present on the brush border of the kidney proximal tubular cells and its inhibition may modify the concentration of peptides in the lumen and have renal effects on patients with diabetes. Meprin ß and high mobility group box-1 protein (HMBGB1) are among the substrates that have been identified as cleaved by DPP-4 and that could play a role in diabetic nephropathy [51]. However, the role of DPP-4-inhibition in meprin or in HMGB1-mediated diabetic nephropathy has not been investigated.

Recently, an antifibrotic effect of the DPP-4 inhibitor linagliptin has been shown in a rodent T1D model of diabetic nephropathy [52]. The mechanism by which linagliptin could exert this antifibrotic effect is through interruption of the cation-independent mannose 6-phosphate receptor (CIM6PR) interaction with transforming growth factor-beta 1 [52].

The renal outcome of the ongoing clinical trial cardiovascular and renal microvascular outcome study with linagliptin in patients with T2D at high vascular risk (CARMELINA) should provide important information on the potential of DPP-4 inhibitors in diabetic nephropathy [53].

References

1 Glaesner W, Vick AM, Millican R, et al. Engineering and characterization of the long-acting glucagon-like peptide-1 analogue LY21189265, an Fc fusion protein. *Diabetes Metab Res Rev*. 2010;26:287-296.

2 Barrington P, Chien JY, Tibaldi F, Showalter HD, Scheneck K, Ellis B. LY21189265, a long-acting glucagon-like peptide-1 analogue showed a dose-dependent effect on insulin secretion in healthy subjects. *Diabetes Obes Metab*. 2011;13:434-438.

3 Wysham C, Blevins T, Arakaki R, et al. Efficacy and Safety of Dulaglutide Added Onto Pioglitazone and Metformin Versus Exenatide in Type 2 Diabet*es in a Randomized* Controlled Trial (AWARD-1). *Diabetes Care*. 2014;37:2159-2167.

4 Lilly Diabetes. Lilly announces positive results of Phase III trials of dulaglutide in type 2 diabetes. https://investor.lilly.com/releasedetall. Accessed October 5, 2015.

5 Umpierrez G ,Povedano ST, Manghi FP, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). *Diabetes Care*. 2014;37:2168-2176.

6 Jendle J, Rosenstock J, Blonde L, et al. Better glycemic control and less weight gain with once-weekly dulaglutide vs once-daily insulin glargine, both combined with pre-meal insulin lispro, in type 2 diabetes patients (AWARD-4). *Diabetes*. 2014;(suppl1):A246-A247.

7 Nauck M, Wistock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). *Diabetes Care*. 2014;37:2149-2158.

8 Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non inferiority trial. *Lancet*. 2014;384:1349-1357.

9 Skrivanek Z, Gaydos BL; Chien JY, et al. Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5). *Diabetes Obes Metab.* 2014 ;16:748-756.

10 Kapitza C, Lynge J, Düring M, Jensen C. Safety, tolerability, pharmacokinetics (PK)/ pharmacodynamics (PD) of single escalating doses of semaglutide, a unique once weekly GLP-1 analogue, in healthy male subjects. *Diabetologia*. 2012;55(suppl1):S341. Abstract 826.

11 Nauck MA, Petrie, JR, Sesti G, et al. The once-weekly human GLP-1 analogue semaglutide provides significant reductions in HbA1c and body weight in patients with type 2 diabetes. *Diabetologia*. 2012;55(suppl 1):S7.

12 Marbury TC, Flint A, Segel S, Lindegaard M, Lasseter K. Pharmacokinetics and tolerability of a single dose of semaglutide, a once-weekly human GLP-1 analog, in subjects with and without renal impairment. *Diabetes*. 2014;63(suppl 1):A260

13 Henry RR, Logan D, Alessi TM Baron MA. A randomized, open-label, multicentre, 4 week study to evaluate the tolerability and pharmacokinetics of ITCA 650, in patients with type 2 diabetes. *Clin Ther*. 2013;35:634-635.

14 Henry RR, Rosenstock J, Logan D, Alessi TM, Lusey K, Baron MA. Randomized trial of continuous subcutaneous delivery of exenatide by ITCA 650 versus twice-daily exenatide injections in metformin-treated type 2 diabetes. *Diabetes Care*. 2013;36:2559-2565.

15 Henry RR, Rosenstock J, Logan D, Alessi TM, Lusey K, Baron MA. Continuous subcutaneous delivery of exenatide via ITCA 650 leads to sustained glycemic control and weight loss for 48 weeks in metformin-treated subjects with type 2 diabetes. *J Diab Comp*. 2014;28:393-398.

16 Alessi T, Henry R, Rosenstock J, Luskey K. Improved patient satisfaction with ITCA 650 vs exenatide injections in subjects with metformin-treated type 2 diabetes. *Diabetologia*. 2011;54(suppl1):S.

17 Intarcia Therapeutics. Intarcia Announces Two Positive Phase 3 Trials for ITCA 650 in Type 2 Diabetes: FREEDOM-1 and FREEDOM-1 High Baseline (HBL) Study Results. intarcia.com/media/press-releases/2015-sep-16-easd.html. Accessed October 5, 2015.

18 Investigation on Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Doses of a Long-acting GLP-1 Analogue in Healthy Male Subjects. https://www.clinicaltrials.gov/ct2/show/NCT01272973. Accessed October 5, 2015.

19 Balena R, Hensley IE, Miller S, Barnett AH. Combination therapy with GLP-1 receptor agonists and basal insulin: a systematic review of the literature. *Diabetes Obes Metab.* 2013;15:485-502.

20 Gough SCL, Buse JB, Woo VC, et al. IDegLira, a novel fixed-ration combination of insulin degludec and liraglutide, is efficacious and safe in subjects with type 2 diabetes: a large, randomized phase 3 trial. *Diabetologia*. 2013;56(suppl1):S96.

21 Gough SCL, Buse JB, Woo VC, et al. One-year efficacy and safety of IDegLira in patients with type 2 diabetes. *Diabetes*. 2014; 63(suppl1): A17.

22 Buse JB, Vilsboll T, Thurman J, et al. Contribution of liraglutide in the fixed-ration combination of insulin degludec and liraglutide (IDegLira). *Diabetes Care*. 2014;37:2926-2933.

23 Rosenstock J, Diamant M, Silvestre L, et al. Benfits of a fixed-ratio of once-daily insulin glargine/lixisenatide (LixiLan) vs glargine in type 2 diabetes (T2DM) inadequately controlled on metformin. *Diabetes*. 2014; 63(suppl1): A87.

24 A Randomized, 30-week, Active-controlled, Open Label, 2- Treatment Arm, Parallel-group, Multicenter Study Comparing the Efficacy and Safety of the Insulin Glargine/Lixisenatide Fixed Ratio Combination to Insulin Glargine With or Without Metformin in Patients With T2DM. http://clinicaltrials.gov/ct2/show/NCT02058160. Accessed October 5, 2015.

25 A Randomized, 30 Week, Active-controlled, Open-label, 3-treatment Arm, Parallel-group Multicenter Study Comparing the Efficacy and Safety of Insulin Glargine/ Lixisenatide Fixed Ratio Combination to Insulin Glargine Alone and to Lixisenatide Alone on Top of Metformin in Patients With Type 2 Diabetes Mellitus T2DM. http://clinicaltrials.gov/ct2/show/NCT02058147. Accessed October 5, 2015.

26 Patel S, DeFronzo A, Lewin D, et al. Fixed dose combinations of empagliflozin/linagliptin for 52 weeks as add-on to metformin in subjects with type 2 diabetes. Presented at: the 50th Meeting of European Association for Study of Diabetes (EASD); Sept 15-19, 2014; Vienna, Austria. www.easdvirtualmeeting.org/resources/19597. Accessed October 5, 2015.

27 A Phase III Randomized, Double-blind, Parallel Group Study to Evaluate the Efficacy and Safety of Once Daily Oral Administration of BI 10773 25 mg/Linagliptin 5 mg and BI 10773 10 mg/ Linagliptin 5 mg Fixed Dose Combination Tablets Compared With the Individual Components (BI 10773 25 mg, BI 10773 10 mg, and Linagliptin 5 mg) for 52 Weeks in Treatment-naïve and Metformin Treated Patients With Type 2 Diabetes Mellitus With Insufficient Glycemic Control. http://clinicaltrials.gov/show/NCT01422876. Accessed October 5, 2015.

28 A Single-dose, Open-label, Randomized, 3 Period, 3 Treatment Crossover Study to Evaluate the Pharmacokinetics of Saxagliptin 5 mg and Dapagliflozin 10 mg When Co-administered to Fasted Healthy Subjects. http://clinicaltrials.gov/show/NCT01662999. Accessed October 5, 2015.

29 A Double-Blind Placebo-Controlled Study of Exenatide for the Treatment of Weight Gain Associated With Olanzapine in Obese Adults With Bipolar Disorder, Major Depressive Disorder, Schizophrenia or Schizoaffective Disorder. http://clinicaltrials.gov/ct2/show/NCT00845507. Accessed October 5, 2015.

30 Lorenz M, Evers A, Wagner M. Recent progress and future options in the development of GLP-1 receptor agonists for the treatment of diabesity. *Bioorg Med Chem Lett.* 2013;23:4011-4018.

31 Panchapakesan U, Mather A, Pollock C. Role of GLP-1 and DPP-4 in diabetic nephropathy and cardiovascular disease. *Clin Sci (London)*. 2013;124:17-26.

32 Astrup A, Carraro R, Harper A, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog liraglutide. *Int J Obesity.* 2012;36:834-854.

33 Sarkar G, Alattar M, Brown RJ, et al. Exenatide treatment for 6 months improves insulin sensitivity in adults with type 1 diabetes. *Diabetes Care*. 2014 37:666-670.

34 Kuhadiya ND, Malik R, Bellini NJ, et al. Liraglutide as additional treatment to insulin in obese patients with type 1 diabetes mellitus. *Endocr Pract*. 2013;19:963-967.

35 Varanasi A1, Bellini N, Rawal D, et al. Liraglutide as additional treatment for type 1 diabetes. *Eur J Endocrinol*. 2011;165:77-84.

36 Ghazi T, Rink L, Sherr JL, Herold KC. Acute metabolic effects of exenatide in patients with Type 1 diabetes with and without residual insulin to oral and IV glucose challenges. *Diabetes Care*. 2014;37:210-216.

37 Albiglutide Versus Placebo in Insulin-treated Subjects With New-onset Type 1 Diabetes Mellitus. https://www.clinicaltrials.gov/ct2/show/NCT02284009. Accessed October 5, 2015.

38 Bose AK, Mocanu MM, Carr RD, et al. Glucagon-like peptide 1 can directly protect the heart againts ischemia/reperfusion injury. *Diabetes*. 2005;54:146-151.

39 Nikolaidis LA, Mankad S, Sokos GG, et al .Effects of glucagon-like peptide-1 in patients with acute myocardial infartion and left ventricular dysfunction after successful reperfusion. *Circulation.* 2004;109:962-965.

40 Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide) (ELIXA). http://clinicaltrials.gov/ct2/ show/NCT01147250. Accessed October 5, 2015.

41 Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results - A Long Term Evaluation (LEADER®). http://clinicaltrials.gov/ct2/show/NCT01179048. Accessed October 5, 2015.

42 Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL): A Trial To Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus. http://clinicaltrials.gov/ct2/show/NCT01144338. Accessed October 5, 2015.

43 Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND). http:// clinicaltrials.gov/ct2/show/NCT01394952. Accessed October 5, 2015.

44 A Study to Evaluate Cardiovascular Outcomes in Patients with Type 2 Diabetes Treated With ITCA 650. www.clinicaltrials.gov/ct2/show/NCT01455896. Accessed October 5, 2015.
45 Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL): A Trial To Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus. http://clinicaltrials.gov/ct2/show/NCT01720446. Accessed October 5, 2015.
46 White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1327-1335.
47 Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317-1326.
48 Sitagliptin Cardiovascular Outcome Study (MK-0431-082) (TECOS). https://clinicaltrials.gov/ct2/show/NCT00790205. Accessed October 5, 2015.
49 CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes. https://clinicaltrials.gov/ct2/show/NCT01243424. Accessed October 5, 2015.
50 Wu S, Hopper I, Skriba M, Krum H. Dipeptidyl-peptidase-4 inhibitors and cardiovascular outcomes: meta-analysis of randomized clinical trials with 55,141 participants. *Cardiovasc Ther*. 2014;32:147-158.
51 Kanasaki K, Shi S, Kanasaki M, et al. Linagliptin-mediated inhibition ameliorates kidney fibrosis in streptozotocin-induced diabetic mica by inhibiting endothelial-to-mesenchymal transition in a therapeutic regimen. *Diabetes*. 2014;63:2120-2131.
52 Panchapakesan U, Pollock CA. DPP-4 inhibitors-renoprotection in diabetic nephropathy? *Diabetes*. 2014;63:1829-1830.
53 Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA). www.clinicaltrials.gov/ct2/show/NCT01272973. Accessed October 5, 2015.